National Toxicology Program
U.S. Department of Health and Human Services

Shift work at Night, Artificial Light at Night, and Circadian Disruption Workshop

Appendix A

Human studies: Cancer, biomarkers, and interventions

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Office of the Report on Carcinogens (ORoC)
Office of Health Assessment and Translation (OHAT)
Division of the National Toxicology Program
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Abstract: Shiftwork at night and transmeridian travel

Background

Multiple human epidemiologic studies of cancer and night shiftwork and time zone or transmeridian travel (TM) have been published since 1972, focusing primarily on breast and prostate cancers. In 2007, the IARC working group concluded that there was limited evidence of increased breast cancer among women working a night shift. Overall, at least 24 studies of the relationship between shiftwork and breast cancer have been studied in large population registries, prospective cohorts, and in nested and population based case control studies. Since the IARC review, in addition to nurses, radio/telegraph operators, geographically based populations, and worker-based population registries, additional populations have been studied in Asia, and Northern and Southern Europe, and in the U.S., Canada, Israel, and Australia have been studied including teachers, national health insurance enrollees, various company based occupational cohorts, twin registries, and controls in large scale clinical trials. Prostate cancer and shiftwork analyses have been conducted in at least 11 general population registries and occupational prospective and retrospective cohorts and population based case-control studies in the U.S., Canada, Germany, Scandinavia, and Japan. In addition, several studies of ovarian, endometrial, colorectal, melanoma, and other cancers have also been investigated in relation to shiftwork.

Studies of breast and prostate cancer in flight attendants and pilots provide some information about the impact of transmeridian travel on the risk of cancer. At least 17 studies of breast cancer in flight attendants from largely retrospective cohorts or registry studies have been conducted in the U.S. and Europe, and approximately 17 registry studies of prostate cancer in airline pilots, cabin attendants, commercial and military pilots, and flightdeck/cockpit crews in U.S., Canada, Sweden, Norway, and Britain.

Exposure assessment

The most common exposure metrics for shift work have included ever working or number of years working night shifts, assessed primarily via self-reported retrospective questionnaires or interview, employment records, or job exposure metrics (e.g., linkages of individual occupational histories with survey data linking occupations to night work). Significant heterogeneity exists in definitions of “shift or night work” across the studies. Most measure night work according to whether participants ever worked nights, the frequency of night shifts worked or the duration of night work (usually in years), but measurements which reflect the biological mechanisms through which shiftwork affects health are found primarily in the newer studies which attempt to assess more detailed information about shift work and relevant potential effect modifiers. Detailed classifications of shiftwork such as regular/irregular shift schedules, time schedules of each shift, intensity, permanent/rotating night shifts, direction and speed of rotation, for example, have been employed in a few studies, such as consecutive night shifts, forward or backward rotations, permanent versus rotating shiftwork, classifications based on time schedules, and exposure window (age at first shift work, or timing before or after full-term pregnancy). The cohort and case-control studies have been able to evaluate potential confounders for breast and prostate cancers, and, more recently, potential

confounders and effect modifiers such as diurnal preference (morning vs. evening type) and genetic susceptibility (polymorphisms in circadian genes).

Most of the studies on flight crew personnel (time zone travel and shift work) have used relatively crude exposure measures (e.g., job title) related to circadian disruption and transmeridian travel, and lack detailed information on potential confounders. Because cosmic radiation and circadian disruption are often correlated in these studies, the independent effect of circadian disruption is difficult to assess. Since 2009, exposure assessment methods for calculating the number of time zones crossed and flight hours worked during the standard sleep hours have been developed (Waters 2009; Grajewski et al. 2011); however, much of the emphasis in current studies has been on the role of cosmic radiation rather than on circadian disruption.

Biomarkers

At least 8 studies of shiftwork and cancer have incorporated measurements of circadian disruption, primarily measurement of 6-sulfatoxymelatonin (aMT6s), the primary urinary metabolite of melatonin and surrogate of circulating melatonin levels. Studies have varied in the sampling and collection of urine (24 hour urine collection or morning urine collection), and recent papers have examined the best timing of melatonin sampling.

The development of markers of circadian disruption which are independent of the time of day, and therefore useful for large population based studies, is currently ongoing.

At least ten studies have compared melatonin levels in urine or blood of day and non-day workers to evaluate the effects of non-day shift work on circadian disruption (e.g., melatonin profiles) and circadian gene expression (e.g., promoter methylation). In addition to melatonin, at least three studies have investigated cortisol in relation to circadian disruption in shift workers; and at least four studies have investigated sex steroid hormones in relation to shiftwork. Markers of immune response and plasma alanine transaminase (ALT) levels have also been investigated.

In addition to evaluating the effects of non-day shift work on melatonin levels, some studies have also looked at associations between urinary melatonin levels and other factors such as ethnicity, reproductive hormones, genetic polymorphisms, gene expression, or methylation. These studies may provide information useful for assessing the cancer epidemiologic studies or evaluating potential mechanisms of carcinogenicity.

Intervention studies

Several studies have examined the impact of changes in direction, speed, length, and other adjustments to rotating shifts on various outcomes related to long-term chronic disease. At least 7 studies describe changes in direction of rotation; six studies describe the impact of switching from 8- to 10- or 12-hour shifts; flexible shift scheduling (1 study); and delayed shift start time (1 study). Two intervention studies investigated changes in markers of circadian disruption; at least five studies investigated markers of chronic disease; and at least 6 studies have looked at the impact of changes on common modifiable risk factors.

Abstract: Artificial light at night

Background

Few human epidemiologic studies of artificial light at night (ALAN) and cancer have been published. Several studies of shiftwork analyzing the risk of various shift work schedules on cancer are essentially estimating the timing of the light/dark cycle or ALAN. So too, some studies of ALAN investigate the impact of the timing of light in the home or sleeping habitat on cancer; while others investigate the intensity or characteristics of light indoors or outdoors (light pollution). The few studies that have been conducted investigate primarily breast and prostate cancers. Overall, 1 prospective cohort and 6 population based case control studies ALAN and breast cancer have been conducted in general populations and non-shift workers in the U.S. northeast, northwest, California and Georgia, Israel, and Western Australia; three studies of breast cancer in relation to rotating schedules among shift workers have been conducted; and, in addition, 4 ecological studies have been conducted of environmental light pollution using satellite images from Israel, Korea, and from 164 countries (updated to 180 countries). Regarding prostate cancer studies, only one case-control study in Western Australia and one ecological study of ALAN using satellite images from 164 countries have been conducted; the latter study also investigated colon and lung cancers.

Exposure assessment

Cohort and case-control studies assess exposure to ALAN primarily by focusing on light in the sleeping habitat via self-reported retrospective questionnaires or interviews, with questions varying widely across studies. Most questions attempt to assess the presence of light in the sleeping habitat (e.g., keeping lights on while sleeping, exposure to outside light, sleeping mainly in the daytime, not drawing the curtains/window shades while sleeping at night, turning lights on during sleep hours, falling asleep with TV on, turning the TV off prior to sleep, use of bed lamps or room lamps for reading before sleep, wearing masks during sleep); while others attempt to assess the intensity of light in the sleeping habitat, such as type of illumination source for bedroom light and reading light (studies show pictures of fluorescent, halogen, and incandescent bulbs), ability to read at night at work, see across the room, to the end of the bed, etc. Light data loggers have been used in a variety of exposure studies to measure the intensity of light; more recently a daysimeter has been developed which measures the light that enters the retina, although methods of use and calibration protocols vary across studies. Bajaj et al. (2011) validated exposure to light assessed with a questionnaire against exposure to light assessed with a daysimeter as the gold standard and found a correlation of 0.7 between the two methods.

Environmental studies of ALAN or studies of exposure to light emitted from multiple environmental sources (street lighting, advertising lighting, architectural lighting, security lighting, domestic lighting and vehicle lighting) have been conducted in geographically defined areas, correlating these measurements with the incidence of breast and other cancers using registry data. In these ecological studies, light and sky glow have been captured by sensors of satellites circling around the globe which transfer information into the U.S. Defense Meteorological Satellite Program’s (US-DMSP GLOBOCAN) database; or have come from aerial surveys and ground-based measurements of direct

illumination and sky glow, including citizen science data. These satellite images constitute a surrogate for exposure to light from multiple sources, and have the goal of ascertaining whether rates of breast cancer are higher in cities with more light, controlling for other macro level factors. These ecological studies are limited by lack of individual level data and potentially uncontrolled confounding, and do not calculate risk estimates. Furthermore, satellite measurements are limited by an incomplete understanding of the relative importance of direct illumination, light scattered by cloud cover and light scattered from a clear sky on circadian disruption, and whether the spectra of light captured in the images are the most relevant for circadian disruption. The relationship of satellite images and actual light in the sleeping area remain to be elucidated (see Rea et al. 2011; Stevens et al. 2011a).

Biomarkers

At least 5 studies have investigated the impact of ALAN on circadian disruption (CD); four used melatonin and one used cortisol as markers of CD. Similar to shift work studies, there have been variations in the sampling and collection of urine across studies.

Intervention studies

Multiple studies of interventions of controlled exposure to light and dark have been conducted. Among shiftworkers, at least 17 studies either controlled exposure to bright light in the workplace (N = 13), or employed goggles to minimize bright light exposure or short wavelengths (N = 4), or both (N = 2). Ten studies looked at sleep quantity or duration as an endpoint, while others measured circadian disruption by measuring melatonin (N = 8), cortisol (N = 2), and/or body temperature (N = 3).

Bibliography

1) Alexander M, Burch JB, Steck SE, Chen CF, Hurley TG, Cavicchia P, Ray M, Shivappa N, Guess J, Zhang H, Youngstedt SD, Creek KE, Lloyd S, Yang X, Hebert JR. 2015. Case-control study of the PERIOD3 clock gene length polymorphism and colorectal adenoma formation. *Oncol Rep* 33(2): 935-941.

2) Anisimov VN, Popovich IG, Zabezhinski MA, Anisimov SV, Vesnushkin GM, Vinogradova IA. 2006. Melatonin as antioxidant, geroprotector and anticarcinogen. *Biochim Biophys Acta* 1757(5-6): 573-589.

3) Arendt J. 2010. Shift work: coping with the biological clock. *Occupational medicine* 60(1): 10-20.

4) Asher G and Sassone-Corsi P. 2015. Time for food: the intimate interplay between nutrition, metabolism, and the circadian clock. *Cell* 161: 84-92

5) Aube M. 2015. Physical behaviour of anthropogenic light propagation into the nocturnal environment. *Philos Trans R Soc Lond B Biol Sci* 370(1667).

6) Bajaj A, Rosner B, Lockley S, Schernhammer ES 2011. Validation of a light questionnaire with real-life photopic illuminance measurements: The Harvard light exposure questionnaire. *Cancer Epidemiol Biomarkers Prev* 20(7): 1341–1349.

7) Bartsch C, Bartsch H, Peschke E. 2009. Light, melatonin and cancer: current results and future perspectives. *Biol Rhythm Res* 40(1): 17-35.

8) Basler M, Jetter A, Fink D, Seifert B, Kullak-Ublick GA, Trojan A. 2014. Urinary excretion of melatonin and association with breast cancer: meta-analysis and review of the literature. *Breast Care (Basel)* 9(3): 182-187.

9) Bauer SE, Wagner SE, Burch J, Bayakly R, Vena JE. 2013. A case-referent study: light at night and breast cancer risk in Georgia. *Int J Health Geogr* 12: 23.

10) Bennie J, Davies TW, Duffy JP, Inger R, Gaston KJ. 2014. Contrasting trends in light pollution across Europe based on satellite observed night time lights. *Sci Rep* 4: 3789.

11) Bhatti P, Cushing-Haugen KL, Wicklund KG, Doherty JA, Rossing MA. 2013. Nightshift work and risk of ovarian cancer. *Occup Environ Med* 70(4): 231-237.

12) Bhatti P, Mirick DK, Davis S. 2013. Racial differences in the association between night shift work and melatonin levels among women. *Am J Epidemiol* 177(5): 388-393.

13) Blask DE, Dauchy RT, Brainard GC, Hanifin JP. 2009. Circadian stage-dependent inhibition of human breast cancer metabolism and growth by the nocturnal melatonin signal: consequences of its disruption by light at night in rats and women. *Integr Cancer Ther* 8(4): 347-353.

14) Bonde JP, Hansen J, Kolstad HA, Mikkelsen S, Olsen JH, Blask DE, Harma M, Kjuus H, de Koning HJ, Olsen J, Moller M, Schernhammer ES, Stevens RG, Akerstedt T. 2012. Work at night and breast cancer--report on evidence-based options for preventive actions. *Scand J Work Environ Health* 38(4): 380-390.

15) Bracci M, Copertaro A, Manzella N, Staffolani S, Strafella E, Nocchi L, Barbaresi M, Copertaro B, Rapisarda V, Valentino M, Santarelli L. 2013. Influence of night-shift and napping at work on urinary melatonin, 17-beta-estradiol and clock gene expression in pre-menopausal nurses. *J Biol Regul Homeost Agents* 27(1): 267-274.

16) Bracci M, Manzella N, Copertaro A, Staffolani S, Strafella E, Barbaresi M, Copertaro B,

Rapisarda V, Valentino M, Santarelli L. 2014. Rotating-shift nurses after a day off: peripheral clock gene expression, urinary melatonin, and serum 17-beta-estradiol levels. *Scand J Work Environ Health* 40(3): 295-304.

17) Brainard GC, Hanifin JP, Warfield B, Stone MK, James ME, Ayers M, Kubey A, Byrne B, Rollag M. 2015. Short-wavelength enrichment of polychromatic light enhances human melatonin suppression potency. *J Pineal Res* 58(3): 352-361.

18) Buja A, Mastrangelo G, Perissinotto E, Grigoletto F, Frigo AC, Rausa G, Marin V, Canova C, Dominici F. 2006. Cancer incidence among female flight attendants: a meta-analysis of published data. *J Womens Health (Larchmt)* 15(1): 98-105.

19) Bullough JD, Rea MS, Figueiro MG. Of mice and women: light as a circadian stimulus in breast cancer research. Cancer Causes Control. 2006 May;17(4):375-83.

20) Bureau of Labor Standards. 2005. Workers on flexible and shift schedules in May 2004. *News: United States Department of Labor.* USDL 05-1198. Friday, July 1, 2005. www.bls.gov/news.release/pdf/flex.pdf

21) Burgess HJ, Molina TA. 2014. Home lighting before usual bedtime impacts circadian timing: a field study. *Photochem Photobiol* 90(3): 723-726.

22) Burgess HJ, Wyatt JK, Park M, Fogg LF. 2015. Home Circadian Phase Assessments with Measures of Compliance Yield Accurate Dim Light Melatonin Onsets. *Sleep* 38(6): 889-897.

23) Burke TM, Markwald RR, Chinoy ED, Snider JA, Bessman SC, Jung CM, Wright KP, Jr. 2013. Combination of light and melatonin time cues for phase advancing the human circadian clock. *Sleep* 36(11): 1617-1624.

24) Buxton OM, Copinschi G, Van Onderbergen A, Karrison TG, Van Cauter E. 2000. A benzodiazepine hypnotic facilitates adaptation of circadian rhythms and sleep-wake homeostasis to an eight hour delay shift simulating westward jet lag. *Sleep* 23(7): 915-927.

25) Carter BD, Diver WR, Hildebrand JS, Patel AV, Gapstur SM. 2014. Circadian disruption and fatal ovarian cancer. *Am J Prev Med* 46(3 Suppl 1): S34-41.

26) Chang AM, Aeschbach D, Duffy JF, Czeisler CA. 2015. Evening use of light-emitting eReaders negatively affects sleep, circadian timing, and next-morning alertness. *Proc Natl Acad Sci U S A* 112(4): 1232-1237.

27) Chang AM, Santhi N, St Hilaire M, Gronfier C, Bradstreet DS, Duffy JF, Lockley SW, Kronauer RE, Czeisler CA. 2012. Human responses to bright light of different durations. *J Physiol* 590(Pt 13): 3103-3112.

28) Chepesiuk R. 2009. Missing the dark: health effects of light pollution. *Environ Health Perspect* 117(1): A20-27.

29) Cho Y, Ryu SH, Lee BR, Kim KH, Lee E, Choi J. 2015. Effects of artificial light at night on human health: A literature review of observational and experimental studies applied to exposure assessment. *Chronobiol Int* 32(9): 1294-1310.

30) Cinzano P, Falchi F, and C.D. Elvidge CD. 2001. The first World Atlas of the artificial night sky brightness. *Mon Not R Astron Soc*. 328: 689-707.

31) Copertaro A, Bracci M, Gesuita R, Carle F, Amati M, Baldassari M, Mocchegiani E, Santarelli L. 2011. Influence of shift-work on selected immune variables in nurses. *Ind*

Health 49(5): 597-604.

32) Costa G, Haus E, Stevens R. 2010. Shift work and cancer - considerations on rationale, mechanisms, and epidemiology. *Scand J Work Environ Health* 36(2): 163-179.

33) Couto P, Miranda D, Vieira R, Vilhena A, De Marco L, Bastos-Rodrigues L. 2014. Association between CLOCK, PER3 and CCRN4L with non‑ small cell lung cancer in Brazilian patients. *Mol Med Rep* 10(1): 435-440.

34) Dai H, Zhang L, Cao M, Song F, Zheng H, Zhu X, Wei Q, Zhang W, Chen K. 2011. The role of polymorphisms in circadian pathway genes in breast tumorigenesis. *Breast Cancer Res Treat* 127(2): 531-540.

35) Davis S, Mirick DK, Chen C, Stanczyk FZ. 2012. Night shift work and hormone levels in women. *Cancer Epidemiol Biomarkers Prev* 21(4): 609-618.

36) Dumont M, Paquet J. 2014. Progressive decrease of melatonin production over consecutive days of simulated night work. *Chronobiol Int* 31(10): 1231-1238.

37) Eastman CI, Molina TA, Dziepak ME, Smith MR. 2012. Blacks (African Americans) have shorter free-running circadian periods than whites (Caucasian Americans). *Chronobiol Int* 29(8): 1072-1077.

38) Emens JS, Burgess HJ. 2015. Effect of Light and Melatonin and Other Melatonin Receptor Agonists on Human Circadian Physiology. *Sleep Med Clin* 10(4): 435-453.

39) Engel P, Fagherazzi G, Mesrine S, Boutron-Ruault MC, Clavel-Chapelon F. 2011. Joint effects of dietary vitamin D and sun exposure on breast cancer risk: results from the French E3N cohort. *Cancer Epidemiol Biomarkers Prev* 20(1): 187-198.

40) Evans JA and Davidson AJ. 2013. Health consequences of circadian disruption in humans and animal models. *Prog Mol Biol Transl Sci*. 119:283-323.

41) Faraut B, Bayon V, Leger D. 2013. Neuroendocrine, immune and oxidative stress in shift workers. *Sleep Med Rev* 17(6): 433-444.

42) Fekedulegn D, Burchfiel CM, Violanti JM, Hartley TA, Charles LE, Andrew ME, Miller DB. 2012. Associations of long-term shift work with waking salivary cortisol concentration and patterns among police officers. *Ind Health* 50(6): 476-486.

43) Fernandez RC Peters S, Carey RN, Davies MJ, Fritschi L. 2014. Assessment of exposure to shiftwork mechanisms in the general population: the development of a new job-exposure matrix. Occup Environ Med 71(10): 723-729.

44) Figueiro MG, Hamner R, Bierman A, Rea MS. Comparisons of three practical field devices used to measure personal light exposures and activity levels. *Lighting Res and Tech* 2013; 45(4): 421-434.

45) Figueiro MG, Rea MS, Bullough JD. Does architectural lighting contribute to breast cancer? *J Carcinogenesis* 2006; 5(1):20.

46) Flynn-Evans EE, Mucci L, Stevens RG, Lockley SW. 2013. Shiftwork and prostate-specific antigen in the National Health and Nutrition Examination Survey. *J Natl Cancer Inst* 105(17): 1292-1297.

47) Fonken LK, Nelson RJ. 2014. The effects of light at night on circadian clocks and metabolism. *Endocr Rev* 35(4): 648-670.

48) Fritschi L, Erren TC, Glass DC, Girschik J, Thomson AK, Saunders C, Boyle T, El-Zaemey S, Rogers P, Peters S, Slevin T, D'Orsogna A, de Vocht F, Vermeulen R,

Heyworth JS. 2013. The association between different night shiftwork factors and breast cancer: a case-control study. *Br J Cancer* 109(9): 2472-2480.

49) Fuhrman BJ, Freedman DM, Bhatti P, Doody MM, Fu YP, Chang SC, Linet MS, Sigurdson AJ. 2013. Sunlight, polymorphisms of vitamin D-related genes and risk of breast cancer. *Anticancer Res* 33(2): 543-551.

50) Gamble KL, Motsinger-Reif AA, Hida A, Borsetti HM, Servick SV, Ciarleglio CM, Robbins S, Hicks J, Carver K, Hamilton N, Wells N, Summar ML, McMahon DG, Johnson CH. 2011. Shift work in nurses: contribution of phenotypes and genotypes to adaptation. *PLoS One* 6(4): e18395.

51) Gaston KJ, Visser ME, Holker F. 2015. The biological impacts of artificial light at night: the research challenge. *Philos Trans R Soc Lond B Biol Sci* 370(1667).

52) Girschik J, Glass D, Ambrosini GL, Fritschi L. 2010. Could mining be protective against prostate cancer? A study and literature review. *Occup Environ Med* 67(6): 365-374.

53) Gomez-Acebo I, Dierssen-Sotos T, Papantoniou K, Garcia-Unzueta MT, Santos-Benito MF, Llorca J. 2015. Association between exposure to rotating night shift versus day shift using levels of 6-sulfatoxymelatonin and cortisol and other sex hormones in women. *Chronobiol Int* 32(1): 128-135.

54) Grajewski B, Waters MA, Yong LC, Tseng CY, Zivkovich Z, Cassinelli RT, 2nd. 2011. Airline pilot cosmic radiation and circadian disruption exposure assessment from logbooks and company records. *Ann Occup Hyg* 55(5): 465-475.

55) Grundy A, Sanchez M, Richardson H, Tranmer J, Borugian M, Graham CH, Aronson KJ. 2009. Light intensity exposure, sleep duration, physical activity, and biomarkers of melatonin among rotating shift nurses. *Chronobiol Int* 26(7): 1443-1461.

56) Grundy A, Schuetz JM, Lai AS, Janoo-Gilani R, Leach S, Burstyn I, Richardson H, Brooks-Wilson A, Spinelli JJ, Aronson KJ. 2013. Shift work, circadian gene variants and risk of breast cancer. *Cancer Epidemiol* 37(5): 606-612.

57) Grundy A, Tranmer J, Richardson H, Graham CH, Aronson KJ. 2011. The influence of light at night exposure on melatonin levels among Canadian rotating shift nurses. *Cancer Epidemiol Biomarkers Prev* 20(11): 2404-2412.

58) Gu F, Han J, Laden F, Pan A, Caporaso NE, Stampfer MJ, Kawachi I, Rexrode KM, Willett WC, Hankinson SE, Speizer FE, Schernhammer ES. 2015. Total and cause-specific mortality of U.S. nurses working rotating night shifts. *Am J Prev Med* 48(3): 241-252.

59) Haim A, Zubidat AE. 2015. Artificial light at night: melatonin as a mediator between the environment and epigenome. *Philos Trans R Soc Lond B Biol Sci* 370(1667).

60) Hammer GP, Blettner M, Zeeb H. 2009. Epidemiological studies of cancer in aircrew. *Radiat Prot Dosimetry* 136(4): 232-239.

61) Hammer GP, Emrich K, Nasterlack M, Blettner M, Yong M. 2015. Shift Work and Prostate Cancer Incidence in Industrial Workers: A Historical Cohort Study in a German Chemical Company. *Dtsch Arztebl Int* 112(27-28): 463-470.

62) Hanlon EC, Van Cauter E. 2011. Quantification of sleep behavior and of its impact on the cross-talk between the brain and peripheral metabolism. Proc Natl Acad Sci U S A. 2011 Sep 13;108 Suppl 3:15609-16.

63) Hansen J, Stevens RG. 2011. Night shiftwork and breast cancer risk: overall evidence. *Occup Environ Med* 68(3): 236.

64) Haus EL, Smolensky MH. 2013. Shift work and cancer risk: potential mechanistic roles of circadian disruption, light at night, and sleep deprivation. *Sleep Med Rev* 17(4): 273-284.

65) He C, Anand ST, Ebell MH, Vena JE, Robb SW. 2015. Circadian disrupting exposures and breast cancer risk: a meta-analysis. *Int Arch Occup Environ Health* 88(5): 533-547.

66) Higuchi S, Nagafuchi Y, Lee SI, Harada T. 2014. Influence of light at night on melatonin suppression in children. *J Clin Endocrinol Metab* 99(9): 3298-3303.

67) Hill SM, Belancio VP, Dauchy RT, Xiang S, Brimer S, Mao L, Hauch A, Lundberg PW, Summers W, Yuan L, Frasch T, Blask DE. 2015. Melatonin: an inhibitor of breast cancer. *Endocr Relat Cancer* 22(3): R183-204.

68) Ho Mien I, Chua EC, Lau P, Tan LC, Lee IT, Yeo SC, Tan SS, Gooley JJ. 2014. Effects of exposure to intermittent versus continuous red light on human circadian rhythms, melatonin suppression, and pupillary constriction. *PLoS One* 9(5): e96532.

69) Hoffman AE, Yi CH, Zheng T, Stevens RG, Leaderer D, Zhang Y, Holford TR, Hansen J, Paulson J, Zhu Y. 2010. CLOCK in breast tumorigenesis: genetic, epigenetic, and transcriptional profiling analyses. *Cancer Res* 70(4): 1459-1468.

70) Hurley S, Goldberg D, Nelson D, Hertz A, Horn-Ross PL, Bernstein L, Reynolds P. 2014. Light at night and breast cancer risk among California teachers. *Epidemiology* 25(5): 697-706.

71) Hurley S, Nelson DO, Garcia E, Gunier R, Hertz A, Reynolds P. 2013. A cross-sectional analysis of light at night, neighborhood sociodemographics and urinary 6-sulfatoxymelatonin concentrations: implications for the conduct of health studies. *Int J Health Geogr* 12: 39.

72) IARC. 2010. Shift work. In *Painting, Firefighting, and Shiftwork*. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, vol. 98. Lyon, France: International Agency for Research on Cancer. p. 563-764.

73) Ijaz S, Verbeek J, Seidler A, Lindbohm ML, Ojajarvi A, Orsini N, Costa G, Neuvonen K. 2013. Night-shift work and breast cancer--a systematic review and meta-analysis. *Scand J Work Environ Health* 39(5): 431-447.

74) Innominato PF, Roche VP, Palesh OG, Ulusakarya A, Spiegel D, Levi FA. 2014. The circadian timing system in clinical oncology. *Ann Med* 46(4): 191-207.

75) Ji BT, Gao YT, Shu XO, Yang G, Yu K, Xue SZ, Li HL, Liao LM, Blair A, Rothman N, Zheng W, Chow WH. 2012. Nightshift work job exposure matrices and urinary 6-sulfatoxymelatonin levels among healthy Chinese women. *Scand J Work Environ Health* 38(6): 553-559.

76) Jia Y, Lu Y, Wu K, Lin Q, Shen W, Zhu M, Huang S, Chen J. 2013. Does night work increase the risk of breast cancer? A systematic review and meta-analysis of epidemiological studies. *Cancer Epidemiol* 37(3): 197-206.

77) Jim HS, Lin HY, Tyrer JP, Lawrenson K, Dennis J, Chornokur G, Chen Z, Chen AY, Permuth-Wey J, Aben KK, Anton-Culver H, Antonenkova N, Bruinsma F, Bandera EV, Bean YT, Beckmann MW, Bisogna M, Bjorge L, Bogdanova N, Brinton LA, Brooks-

Wilson A, Bunker CH, Butzow R, Campbell IG, Carty K, Chang-Claude J, Cook LS, Cramer DW, Cunningham JM, Cybulski C, Dansonka-Mieszkowska A, du Bois A, Despierre E, Sieh W, Doherty JA, Dork T, Durst M, Easton DF, Eccles DM, Edwards RP, Ekici AB, Fasching PA, Fridley BL, Gao YT, Gentry-Maharaj A, Giles GG, Glasspool R, Goodman MT, Gronwald J, Harter P, Hasmad HN, Hein A, Heitz F, Hildebrandt MA, Hillemanns P, Hogdall CK, Hogdall E, Hosono S, Iversen ES, Jakubowska A, Jensen A, Ji BT, Karlan BY, Kellar M, Kiemeney LA, Krakstad C, Kjaer SK, Kupryjanczyk J, Vierkant RA, Lambrechts D, Lambrechts S, Le ND, Lee AW, Lele S, Leminen A, Lester J, Levine DA, Liang D, Lim BK, Lissowska J, Lu K, Lubinski J, Lundvall L, Massuger LF, Matsuo K, McGuire V, McLaughlin JR, McNeish I, Menon U, Milne RL, Modugno F, Thomsen L, Moysich KB, Ness RB, Nevanlinna H, Eilber U, Odunsi K, Olson SH, Orlow I, Orsulic S, Palmieri Weber R, Paul J, Pearce CL, Pejovic T, Pelttari LM, Pike MC, Poole EM, Schernhammer E, Risch HA, Rosen B, Rossing MA, Rothstein JH, Rudolph A, Runnebaum IB, Rzepecka IK, Salvesen HB, Schwaab I, Shu XO, Shvetsov YB, Siddiqui N, Song H, Southey MC, Spiewankiewicz B, Sucheston-Campbell L, Teo SH, Terry KL, Thompson PJ, Tangen IL, Tworoger SS, van Altena AM, Vergote I, Walsh CS, Wang-Gohrke S, Wentzensen N, Whittemore AS, Wicklund KG, Wilkens LR, Wu AH, Wu X, Woo YL, Yang H, Zheng W, Ziogas A, Amankwah E, Berchuck A, Georgia Chenevix-Trench on behalf of the Amg, Schildkraut JM, Kelemen LE, Ramus SJ, Monteiro AN, Goode EL, Narod SA, Gayther SA, Pharoah PD, Sellers TA, Phelan CM. 2015. Common Genetic Variation in Circadian Rhythm Genes and Risk of Epithelial Ovarian Cancer (EOC). *J Genet Genome Res* 2(2).

78) Johnson CY, Grajewski B. 2015. Bias from Differential Exposure Measurement Error in a Study of Flight Attendants. *Aerosp Med Hum Perform* 86(11): 990-993.

79) Jones TM, Durrant J, Michaelides EB, Green MP. 2015. Melatonin: a possible link between the presence of artificial light at night and reductions in biological fitness. *Philos Trans R Soc Lond B Biol Sci* 370(1667).

80) Jung-Hynes B, Huang W, Reiter RJ, Ahmad N. 2010. Melatonin resynchronizes dysregulated circadian rhythm circuitry in human prostate cancer cells. *J Pineal Res* 49(1): 60-68.

81) Kamdar BB, Tergas AI, Mateen FJ, Bhayani NH, Oh J. 2013. Night-shift work and risk of breast cancer: a systematic review and meta-analysis. *Breast Cancer Res Treat* 138(1): 291-301.

82) Kantermann T, Sung H, Burgess HJ. 2015. Comparing the Morningness-Eveningness Questionnaire and Munich ChronoType Questionnaire to the Dim Light Melatonin Onset. *J Biol Rhythms* 30(5): 449-453.

83) Karantanos T, Theodoropoulos G, Gazouli M, Vaiopoulou A, Karantanou C, Stravopodis DJ, Bramis K, Lymperi M, Pektasidis D. 2013. Association of the clock genes polymorphisms with colorectal cancer susceptibility. *J Surg Oncol* 108(8): 563-567.

84) Kennaway DJ. 2014. Light at night, melatonin and breast cancer. *Chronobiol Int* 31(2): 297-298.

85) Keshet-Sitton A, Or-Chen K, Yitzhak S, Tzabary I, Haim A. 2015. Can Avoiding Light at Night Reduce the Risk of Breast Cancer? *Integr Cancer Ther*.

86) Kettner NM, Katchy CA, Fu L. 2014. Circadian gene variants in cancer. *Ann Med* 46(4): 208-220.

87) Khaleghipour S, Masjedi M, Kelishadi R. 2015. Circadian type, chronic fatigue, and serum IgM in the shift workers of an industrial organization. *Adv Biomed Res* 4: 61.

88) Kim SJ, Benloucif S, Reid KJ, Weintraub S, Kennedy N, Wolfe LF, Zee PC. 2014. Phase-shifting response to light in older adults. *J Physiol* 592(Pt 1): 189-202.

89) Kim YJ, Park MS, Lee E, Choi JW. 2016. High Incidence of Breast Cancer in Light-Polluted Areas with Spatial Effects in Korea. *Asian Pac J Cancer Prev* 17(1): 361-367.

90) Klerman EB, Gershengorn HB, Duffy JF, Kronauer RE. 2002. Comparisons of the variability of three markers of the human circadian pacemaker. *J Biol Rhythms* 17(2): 181-193.

91) Kloog I, Haim A, Stevens RG, Barchana M, Portnov BA. 2008. Light at night co-distributes with incident breast but not lung cancer in the female population of Israel. *Chronobiol Int* 25(1): 65-81.

92) Kloog I, Portnov BA, Rennert HS, Haim A. 2011. Does the modern urbanized sleeping habitat pose a breast cancer risk? *Chronobiol Int* 28(1): 76-80.

93) Kloog I, Stevens RG, Haim A, Portnov BA. 2010. Nighttime light level co-distributes with breast cancer incidence worldwide. *Cancer Causes Control* 21(12): 2059-2068.

94) Kolstad HA. Nightshift work and risk of breast cancer and other cancers--a critical review of the epidemiologic evidence. Scand J Work Environ Health. 2008. Feb 34(1):5-22.

95) Kosir R, Spaninger K, Rozman D. 2013. Circadian events in human diseases and in cytochrome P450-related drug metabolism and therapy. *IUBMB Life* 65(6): 487-496.

96) Kotsopoulos J, Tworoger SS, Campos H, Chung FL, Clevenger CV, Franke AA, Mantzoros CS, Ricchiuti V, Willett WC, Hankinson SE, Eliassen AH. 2010. Reproducibility of plasma and urine biomarkers among premenopausal and postmenopausal women from the Nurses' Health Studies. *Cancer Epidemiol Biomarkers Prev* 19(4): 938-946.

97) Kozaki T, Kubokawa A, Taketomi R, Hatae K. 2015. Effects of day-time exposure to different light intensities on light-induced melatonin suppression at night. *J Physiol Anthropol* 34: 27.

98) Kozaki T, Kubokawa A, Taketomi R, Hatae K. 2016. Light-induced melatonin suppression at night after exposure to different wavelength composition of morning light. *Neurosci Lett* 616: 1-4.

99) Krugluger W, Brandstaetter A, Kallay E, Schueller J, Krexner E, Kriwanek S, Bonner E, Cross HS. 2007. Regulation of genes of the circadian clock in human colon cancer: reduced period-1 and dihydropyrimidine dehydrogenase transcription correlates in high-grade tumors. *Cancer Res* 67(16): 7917-7922.

100) Kwon P, Lundin J, Li W, Ray R, Littell C, Gao D, Thomas DB, Checkoway H. 2015. Night shift work and lung cancer risk among female textile workers in Shanghai, China. *J Occup Environ Hyg* 12(5): 334-341.

101) Labrecque N, Cermakian N. 2015. Circadian Clocks in the Immune System. *J Biol Rhythms* 30(4): 277-290.

102) Langley AR, Graham CH, Grundy AL, Tranmer JE, Richardson H, Aronson KJ. 2012. A cross-sectional study of breast cancer biomarkers among shift working nurses. *BMJ Open*

2(1): e000532.

103) Leonardi GC, Rapisarda V, Marconi A, Scalisi A, Catalano F, Proietti L, Travali S, Libra M, Fenga C. 2012. Correlation of the risk of breast cancer and disruption of the circadian rhythm (Review). *Oncol Rep* 28(2): 418-428.

104) Leproult R, Holmbäck U, Van Cauter E. 2014. Circadian misalignment augments markers of insulin resistance and inflammation, independently of sleep loss. Diabetes. 2014 Jun;63(6):1860-9.

105) Lewy AJ, Emens J, Jackman A, Yuhas K. 2006. Circadian uses of melatonin in humans. *Chronobiol Int* 23(1-2): 403-412.

106) Lewy AJ, Sack RL, Blood ML, Bauer VK, Cutler NL, Thomas KH. 1995. Melatonin marks circadian phase position and resets the endogenous circadian pacemaker in humans. *Ciba Found Symp* 183: 303-317; discussion 317-321.

107) Li Q, Zheng T, Holford TR, Boyle P, Zhang Y, Dai M. 2010. Light at night and breast cancer risk: results from a population-based case-control study in Connecticut, USA. *Cancer Causes Control* 21(12): 2281-2285.

108) Lie JA, Kjuus H, Zienolddiny S, Haugen A, Kjaerheim K. 2013. Breast cancer among nurses: is the intensity of night work related to hormone receptor status? *Am J Epidemiol* 178(1): 110-117.

109) Lin X, Chen W, Wei F, Ying M, Wei W, Xie X. 2015b. Night-shift work increases morbidity of breast cancer and all-cause mortality: a meta-analysis of 16 prospective cohort studies. *Sleep Med* 16(11): 1381-1387.

110) Liu R, Jacobs DI, Hansen J, Fu A, Stevens RG, Zhu Y. 2015. Aberrant methylation of miR-34b is associated with long-term shiftwork: a potential mechanism for increased breast cancer susceptibility. *Cancer Causes Control* 26(2): 171-178.

111) Lowden A, Akerstedt T. 1998. Retaining home-base sleep hours to prevent jet lag in connection with a westward flight across nine time zones. *Chronobiol Int* 15(4): 365-376.

112) Madden MH, Anic GM, Thompson RC, Nabors LB, Olson JJ, Browning JE, Monteiro AN, Egan KM. 2014. Circadian pathway genes in relation to glioma risk and outcome. *Cancer Causes Control* 25(1): 25-32.

113) Markt SC, Valdimarsdottir UA, Shui IM, Sigurdardottir LG, Rider JR, Tamimi RM, Batista JL, Haneuse S, Flynn-Evans E, Lockley SW, Czeisler CA, Stampfer MJ, Launer L, Harris T, Smith AV, Gudnason V, Lindstrom S, Kraft P, Mucci LA. 2015. Circadian clock genes and risk of fatal prostate cancer. *Cancer Causes Control* 26(1): 25-33.

114) Matheson A, O'Brien L, Reid JA. The impact of shiftwork on health: a literature review. 2014. *J Clin Nurs.* 23(23-24): 3309-20.

115) Megdal SP, Kroenke CH, Laden F, Pukkala E, Schernhammer ES. 2005. Night work and breast cancer risk: a systematic review and meta-analysis. *Eur J Cancer* 41(13): 2023-2032.

116) Mirick DK, Bhatti P, Chen C, Nordt F, Stanczyk FZ, Davis S. 2013. Night shift work and levels of 6-sulfatoxymelatonin and cortisol in men. *Cancer Epidemiol Biomarkers Prev* 22(6): 1079-1087.

117) Mistlberger RE, Skene DJ. 2005. Nonphotic entrainment in humans? *J Biol Rhythms* 20(4): 339-352.

118) Neil-Sztramko SE, Pahwa M, Demers PA, Gotay CC. 2014. Health-related interventions among night shift workers: a critical review of the literature. *Scand J Work Environ Health* 40(6): 543-556.

119) Niu SF, Chung MH, Chu H, Tsai JC, Lin CC, Liao YM, Ou KL, O'Brien AP, Chou KR. 2015. Differences in cortisol profiles and circadian adjustment time between nurses working night shifts and regular day shifts: A prospective longitudinal study. *Int J Nurs Stud* 52(7): 1193-1201.

120) Obayashi K, Saeki K, Iwamoto J, Okamoto N, Tomioka K, Nezu S, Ikada Y, Kurumatani N. 2012. Positive effect of daylight exposure on nocturnal urinary melatonin excretion in the elderly: a cross-sectional analysis of the HEIJO-KYO study. *J Clin Endocrinol Metab* 97(11): 4166-4173.

121) Oh JH, Yoo H, Park HK, Do YR. 2015. Analysis of circadian properties and healthy levels of blue light from smartphones at night. *Sci Rep* 5: 11325.

122) Opperhuizen AL, van Kerkhof LWM, Proper KI, Rodenburg W and Kalsbeek A. 2015. Rodent models to study the metabolic effects of shiftwork in humans. *Front. Pharmacol*. 6:50.

123) Ortiz-Tudela E, Mteyrek A, Ballesta A, Innominato PF, Levi F. 2013. Cancer chronotherapeutics: experimental, theoretical, and clinical aspects. *Handb Exp Pharmacol*(217): 261-288.

124) Papantoniou K, Castano-Vinyals G, Espinosa A, Aragones N, Perez-Gomez B, Burgos J, Gomez-Acebo I, Llorca J, Peiro R, Jimenez-Moleon JJ, Arredondo F, Tardon A, Pollan M, Kogevinas M. 2015a. Night shift work, chronotype and prostate cancer risk in the MCC-Spain case-control study. *Int J Cancer* 137(5): 1147-1157.

125) Papantoniou K, Castano-Vinyals G, Espinosa A, Aragones N, Perez-Gomez B, Ardanaz E, Altzibar JM, Sanchez VM, Gomez-Acebo I, Llorca J, Munoz D, Tardon A, Peiro R, Marcos-Gragera R, Pollan M, Kogevinas M. 2015b. Breast cancer risk and night shift work in a case-control study in a Spanish population. *Eur J Epidemiol*.

126) Papantoniou K, Pozo OJ, Espinosa A, Marcos J, Castano-Vinyals G, Basagana X, Ribas FC, Mirabent J, Martin J, Carenys G, Martin CR, Middleton B, Skene DJ, Kogevinas M. 2014. Circadian variation of melatonin, light exposure, and diurnal preference in day and night shift workers of both sexes. *Cancer Epidemiol Biomarkers Prev* 23(7): 1176-1186.

127) Pijpe A, Slottje P, van Pelt C, Stehmann F, Kromhout H, van Leeuwen FE, Vermeulen RC, Rookus MA. 2014. The Nightingale study: rationale, study design and baseline characteristics of a prospective cohort study on shift work and breast cancer risk among nurses. *BMC Cancer* 14: 47.

128) Poole EM, Schernhammer ES, Tworoger SS. 2011. Rotating night shift work and risk of ovarian cancer. *Cancer Epidemiol Biomarkers Prev* 20(5): 934-938.

129) Poole EM, Schernhammer E, Mills L, Hankinson SE, Tworoger SS. 2015. Urinary melatonin and risk of ovarian cancer. Cancer Causes Control. Oct 26(10): 1501-6.

130) Qiu J, Yang R, Rao Y, Du Y, Kalembo FW. 2012. Risk factors for breast cancer and expression of insulin-like growth factor-2 (IGF-2) in women with breast cancer in Wuhan City, China. *PLoS One* 7(5): e36497.

131) Rabstein S, Harth V, Justenhoven C, Pesch B, Plottner S, Heinze E, Lotz A, Baisch C, Schiffermann M, Brauch H, Hamann U, Ko Y, Bruning T, Consortium G. 2014.

Polymorphisms in circadian genes, night work and breast cancer: results from the GENICA study. *Chronobiol Int* 31(10): 1115-1122.

132) Ramin C, Devore EE, Pierre-Paul J, Duffy JF, Hankinson SE, Schernhammer ES. 2013. Chronotype and breast cancer risk in a cohort of US nurses. *Chronobiol Int* 30(9): 1181-1186.

133) Ramin CA, Massa J, Wegrzyn LR, Brown SB, Pierre-Paul J, Devore EE, Hankinson SE, Schernhammer ES. 2015. The association of body size in early to mid-life with adult urinary 6-sulfatoxymelatonin levels among night shift health care workers. *BMC Public Health* 15: 467.

134) Rana S, Munawar M, Shahid A, Malik M, Ullah H, Fatima W, Mohsin S, Mahmood S. 2014b. Deregulated expression of circadian clock and clock-controlled cell cycle genes in chronic lymphocytic leukemia. *Mol Biol Rep* 41(1): 95-103.

135) Rana S, Shahid A, Ullah H, Mahmood S. 2014a. Lack of association of the NPAS2 gene Ala394Thr polymorphism (rs2305160:G>A) with risk of chronic lymphocytic leukemia. *Asian Pac J Cancer Prev* 15(17): 7169-7174.

136) Rao D, Yu H, Bai Y, Zheng X, Xie L. 2015. Does night-shift work increase the risk of prostate cancer? a systematic review and meta-analysis. *Onco Targets Ther* 8: 2817-2826.

137) Raslau D, Summerfield DT, Abu Dabrh AM, Steinkraus LW, Murad MH. 2015. The risk of prostate cancer in pilots: a meta-analysis. *Aerosp Med Hum Perform* 86(2): 112-117.

138) Rea MS, Brons JA, Figueiro MG. 2011. Measurements of light at night (LAN) for a sample of female school teachers. *Chronobiol Int* 28(8): 673-680.

139) Rea MS, Bierman A, Figueiro MG, Bullough JD. 2008. A new approach to understanding the impact of circadian disruption on human health. *Journal of Circadian Rhythms* 6:7.

140) Rea MS, Figueiro MG. 2014. Quantifying light-dependent circadian disruption in humans and animal models. *Chronobiol Int* 31(10): 1239-1246.

141) Reinhardt EL, Fernandes PA, Markus RP, Fischer FM. 2012. Daily rhythm of salivary IL-1ss, cortisol and melatonin in day and night workers. *Work* 41 Suppl 1: 5788-5790.

142) Reiter, R. J. (1985) Action spectra, dose-response relationships, and temporal aspects of light's effects on the pineal gland. Ann NY Acad Sci 453, 215-230.

143) Reiter RJ, Tan DX, Korkmaz A, Erren TC, Piekarski C, Tamura H, Manchester LC. 2007. Light at night, chronodisruption, melatonin suppression, and cancer risk: a review. *Crit Rev Oncog* 13(4): 303-328.

144) Reszka E, Peplonska B, Wieczorek E, Sobala W, Bukowska A, Gromadzinska J, Lie JA, Kjuus H, Wasowicz W. 2013. Circadian gene expression in peripheral blood leukocytes of rotating night shift nurses. *Scand J Work Environ Health* 39(2): 187-194.

145) Rybnikova N, Haim A, Portnov BA. 2015. Artificial Light at Night (ALAN) and breast cancer incidence worldwide: A revisit of earlier findings with analysis of current trends. *Chronobiol Int* 32(6): 757-773.

146) Sanlorenzo M, Wehner MR, Linos E, Kornak J, Kainz W, Posch C, Vujic I, Johnston K, Gho D, Monico G, McGrath JT, Osella-Abate S, Quaglino P, Cleaver JE, Ortiz-Urda S. 2015. The risk of melanoma in airline pilots and cabin crew: a meta-analysis. *JAMA Dermatol* 151(1): 51-58.

147) Sano I, Tanito M, Okuno T, Ishiba Y, Ohira A. 2014. Estimation of the melatonin suppression index through clear and yellow-tinted intraocular lenses. *Jpn J Ophthalmol* 58(4): 320-326.

148) Schernhammer ES, Berrino F, Krogh V, Secreto G, Micheli A, Venturelli E, Grioni S, Sempos CT, Cavalleri A, Schunemann HJ, Strano S, Muti P. 2010. Urinary 6-Sulphatoxymelatonin levels and risk of breast cancer in premenopausal women: the ORDET cohort. *Cancer Epidemiol Biomarkers Prev* 19(3): 729-737.

149) Schernhammer ES, Berrino F, Krogh V, Secreto G, Micheli A, Venturelli E, Sieri S, Sempos CT, Cavalleri A, Schunemann HJ, Strano S, Muti P. 2008. Urinary 6-sulfatoxymelatonin levels and risk of breast cancer in postmenopausal women. *J Natl Cancer Inst* 100(12): 898-905.

150) Schernhammer ES, Feskanich D, Niu C, Dopfel R, Holmes MD, Hankinson SE. 2009. Dietary correlates of urinary 6-sulfatoxymelatonin concentrations in the Nurses' Health Study cohorts. *Am J Clin Nutr* 90(4): 975-985.

151) Schernhammer ES, Hankinson SE. 2009. Urinary melatonin levels and postmenopausal breast cancer risk in the Nurses' Health Study cohort. *Cancer Epidemiol Biomarkers Prev* 18(1): 74-79.

152) Schubauer-Berigan MK, Anderson JL, Hein MJ, Little MP, Sigurdson AJ, Pinkerton LE. 2015. Breast cancer incidence in a cohort of U.S. flight attendants. *Am J Ind Med* 58(3): 252-266.

153) Serkh K, Forger DB. 2014. Optimal schedules of light exposure for rapidly correcting circadian misalignment. *PLoS Comput Biol* 10(4): e1003523.

154) Sigurdardottir LG, Valdimarsdottir UA, Fall K, Rider JR, Lockley SW, Schernhammer E, Mucci LA. 2012. Circadian disruption, sleep loss, and prostate cancer risk: a systematic review of epidemiologic studies. *Cancer Epidemiol Biomarkers Prev* 21(7): 1002-1011.

155) Skene DJ, Bojkowski CJ, Currie JE, Wright J, Boulter PS, Arendt J. 1990. 6-sulphatoxymelatonin production in breast cancer patients. *J Pineal Res* 8(3): 269-276.

156) Smith MR, Burgess HJ, Fogg LF, Eastman CI. 2009. Racial differences in the human endogenous circadian period. *PLoS One* 4(6): e6014.

157) Smolensky MH, Sackett-Lundeen LL, Portaluppi F. 2015. Nocturnal light pollution and underexposure to daytime sunlight: Complementary mechanisms of circadian disruption and related diseases. *Chronobiol Int* 32(8): 1029-1048.

158) Stevens RG and Rea MS. 2001. Light in the Built Environment: Potential Role of Circadian Disruption in Endocrine Disruption and Breast Cancer. *Cancer Causes & Control*, 12(3): 279-287.

159) Stevens RG. 2009c. Light-at-night, circadian disruption and breast cancer: assessment of existing evidence. *Int J Epidemiol* 38(4): 963-970.

160) Stevens RG. 2011a. Testing the light-at-night (LAN) theory for breast cancer causation. *Chronobiol Int.* 28(8): 653-656.

161) Stevens RG, Hansen J, Costa G, Haus E, Kauppinen T, Aronson KJ, Castano-Vinyals G, Davis S, Frings-Dresen MH, Fritschi L, Kogevinas M, Kogi K, Lie JA, Lowden A, Peplonska B, Pesch B, Pukkala E, Schernhammer E, Travis RC, Vermeulen R, Zheng T, Cogliano V, Straif K. 2011b. Considerations of circadian impact for defining 'shift work'

in cancer studies: IARC Working Group Report. *Occup Environ Med* 68(2): 154-162.

162) Stevens RG, Hansen J, Schernhammer ES, Davis S. 2013b. Response to Ijaz S, et al. "Night-shift work and breast cancer--a systematic review and meta-analysis". *Scand J Work Environ Health* 39(6): 631-632.

163) Stevens RG, Brainard GC, Blask DE, Lockley SW, Motta ME. 2014. Breast cancer and circadian disruption from electric lighting in the modern world. *CA Cancer J Clin* 64(3): 207-218.

164) Stevens RG, Zhu Y. 2015. Electric light, particularly at night, disrupts human circadian rhythmicity: is that a problem? *Philos Trans R Soc Lond B Biol Sci* 370(1667).

165) Stone EL, Wakefield A, Harris S, Jones G. 2015. The impacts of new street light technologies: experimentally testing the effects on bats of changing from low-pressure sodium to white metal halide. *Philos Trans R Soc Lond B Biol Sci* 370(1667).

166) Suba Z. 2012. Light deficiency confers breast cancer risk by endocrine disorders. *Recent Pat Anticancer Drug Discov* 7(3): 337-344.

167) Summa K.C., Turek, F.W. (2014) Biomedical Effects of Circadian Rhythm Disturbances, Chapter 4 in Impact of Sleep and Sleep Disturbances on Obesity and Cancer. (S. Redline & N.A. Berger, eds.). Springer Science+Business Media, New York, pp. 77-99.

168) Ticher A, Haus E, Ron IG, Sackett-Lundeen L, Ashkenazi IE. 1996. The pattern of hormonal circadian time structure (acrophase) as an assessor of breast-cancer risk. *Int J Cancer* 65(5): 591-593.

169) Truong T, Liquet B, Menegaux F, Plancoulaine S, Laurent-Puig P, Mulot C, Cordina-Duverger E, Sanchez M, Arveux P, Kerbrat P, Richardson S, Guenel P. 2014. Breast cancer risk, nightwork, and circadian clock gene polymorphisms. *Endocr Relat Cancer* 21(4): 629-638.

170) van der Rhee H, Coebergh JW, de Vries E. 2013. Is prevention of cancer by sun exposure more than just the effect of vitamin D? A systematic review of epidemiological studies. *Eur J Cancer* 49(6): 1422-1436.

171) Van Dycke KC, Rodenburg W, van Oostrom CT, van Kerkhof LW, Pennings JL, Roenneberg T, van Steeg H, van der Horst GT. 2015a. Chronically Alternating Light Cycles Increase Breast Cancer Risk in Mice. *Curr Biol* 25(14): 1932-1937

172) Van Dycke KC, Pennings JL, van Oostrom CT, van Kerkhof LW, van Steeg H, van der Horst GT, Rodenburg W. 2015b. Biomarkers for circadian rhythm disruption independent of time of day. *PLoS One* 10(5): e0127075.

173) van Mark A, Weiler SW, Schroder M, Otto A, Jauch-Chara K, Groneberg DA, Spallek M, Kessel R, Kalsdorf B. 2010. The impact of shift work induced chronic circadian disruption on IL-6 and TNF-alpha immune responses. *J Occup Med Toxicol* 5: 18.

174) Viswanathan AN, Schernhammer ES. 2009. Circulating melatonin and the risk of breast and endometrial cancer in women. *Cancer Lett* 281(1): 1-7.

175) Wada K, Nagata C, Nakamura K, Iwasa S, Shiraki M, Shimizu H. 2012. Light exposure at night, sleep duration and sex hormone levels in pregnant Japanese women. *Endocr J* 59(5): 393-398.

176) Wang F, Yeung KL, Chan WC, Kwok CC, Leung SL, Wu C, Chan EY, Yu IT, Yang XR, Tse LA. 2013a. A meta-analysis on dose-response relationship between night shift work

and the risk of breast cancer. *Ann Oncol* 24(11): 2724-2732.

177) Wang WM, Yuan P, Wang JY, Ma F, Fan Y, Li Q, Zhang P, Xu BH. 2013b. [Association of genetic variantions of circadian clock genes and risk of breast cancer]. *Zhonghua Zhong Liu Za Zhi* 35(3): 236-239.

178) Wang X, Ji A, Zhu Y, Liang Z, Wu J, Li S, Meng S, Zheng X, Xie L. 2015. A meta-analysis including dose-response relationship between night shift work and the risk of colorectal cancer. *Oncotarget* 6(28): 25046-25060.

179) Wang XS, Armstrong ME, Cairns BJ, Key TJ, Travis RC. 2011. Shift work and chronic disease: the epidemiological evidence. *Occup Med (Lond)* 61(2): 78-89.

180) Waters MA, Grajewski B, Pinkerton LE, Hein MJ, Zivkovich Z. 2009. Development of historical exposure estimates of cosmic radiation and circadian rhythm disruption for cohort studies of Pan Am flight attendants. *Am J Ind Med* 52(10): 751-761.

181) Wirth M, Burch J, Violanti J, Burchfiel C, Fekedulegn D, Andrew M, Zhang H, Miller DB, Youngstedt SD, Hebert JR, Vena JE. 2013. Association of the Period3 clock gene length polymorphism with salivary cortisol secretion among police officers. *Neuro Endocrinol Lett* 34(1): 27-37.

182) Wirth MD, Burch J, Shivappa N, Steck SE, Hurley TG, Vena JE, Hebert JR. 2014c. Dietary inflammatory index scores differ by shift work status: NHANES 2005 to 2010. *J Occup Environ Med* 56(2): 145-148.

183) Wirth MD, Burch J, Shivappa N, Violanti JM, Burchfiel CM, Fekedulegn D, Andrew ME, Hartley TA, Miller DB, Mnatsakanova A, Charles LE, Steck SE, Hurley TG, Vena JE, Hebert JR. 2014a. Association of a dietary inflammatory index with inflammatory indices and metabolic syndrome among police officers. *J Occup Environ Med* 56(9): 986-989.

184) Wirth MD, Burch JB, Hebert JR, Kowtal P, Mehrotra-Kapoor A, Steck SE, Hurley TG, Gupta PC, Pednekar MS, Youngstedt SD, Zhang H, Sarin R. 2014b. Case-control study of breast cancer in India: Role of PERIOD3 clock gene length polymorphism and chronotype. *Cancer Invest* 32(7): 321-329.

185) Wood B, Rea MS, Plitnick B, Figueiro MG. 2013. Light level and duration of exposure determine the impact of self-luminous tablets on melatonin suppression. *Appl Ergon* 44(2): 237-240.

186) Yong LC, Pinkerton LE, Yiin JH, Anderson JL, Deddens JA. 2014. Mortality among a cohort of U.S. commercial airline cockpit crew. *Am J Ind Med* 57(8): 906-914.

187) Yu EA, Weaver DR. 2011. Disrupting the circadian clock: gene-specific effects on aging, cancer, and other phenotypes. *Aging (Albany NY)* 3(5): 479-493.

188) Zamanian Z, Kakooei H, Ayattollahi SM, Dehghani M. 2010. Effect of bright light on shift work nurses in hospitals. *Pak J Biol Sci* 13(9): 431-436.

189) Zee PC, Goldstein CA. 2010. Treatment of shift work disorder and jet lag. *Curr Treat Options Neurol* 12(5): 396-411.

190) Zeitzer JM, Nouriani B, Neri E, Spiegel D. 2014. Correspondence of plasma and salivary cortisol patterns in women with breast cancer. *Neuroendocrinology* 100(2-3): 153-161.

191) Zhao B, Lu J, Yin J, Liu H, Guo X, Yang Y, Ge N, Zhu Y, Zhang H, Xing J. 2012. A functional polymorphism in PER3 gene is associated with prognosis in hepatocellular

carcinoma. *Liver Int* 32(9): 1451-1459.

192) Zhou F, He X, Liu H, Zhu Y, Jin T, Chen C, Qu F, Li Y, Bao G, Chen Z, Xing J. 2012. Functional polymorphisms of circadian positive feedback regulation genes and clinical outcome of Chinese patients with resected colorectal cancer. *Cancer* 118(4): 937-946.

193) Zhu Y, Stevens RG, Hoffman AE, Tjonneland A, Vogel UB, Zheng T, Hansen J. 2011. Epigenetic impact of long-term shiftwork: pilot evidence from circadian genes and whole-genome methylation analysis. *Chronobiol Int* 28(10): 852-861.

194) Zhu Y, Zheng T, Stevens RG, Zhang Y, Boyle P. 2006. Does "clock" matter in prostate cancer? *Cancer Epidemiol Biomarkers Prev* 15(1): 3-5.

195) Zienolddiny S, Haugen A, Lie JA, Kjuus H, Anmarkrud KH, Kjaerheim K. 2013. Analysis of polymorphisms in the circadian-related genes and breast cancer risk in Norwegian nurses working night shifts. *Breast Cancer Res* 15(4): R53.

Table 1. Epidemiologic studies of Breast Cancer and circadian disruption: meta-analyses, study populations, exposure metrics, and counfounders or effect modifiers

	Circadian Disruption Proxies			
	Studies of shift workers and shift rotations	**Flight attendants - Transmeridian travel**	**Chronotype as main exposure**	**Artificial Light at Night (ALAN) - impact of the timing and intensity/type of ALAN**
Meta-analyses (No. studies)	Lin X et al. 2015 (16); He et al. 2015 (15); Ijaz et al. 2013 (16); Jia et al. 2013 (13); Kamdar et al. 2013 (15); Wang et al. 2013 (10); Yong et al. 2012 (5); Bonde et al. 2012; Megdal et al. 2005(6); Davis S et al. 2006 (potential for genetic polymorphisms to play a role)	He et al. 2015 (3); Gassmann AS et al. 2015 (17); Buja et al. 2006 (7); Megdal et al. 2005 (7); Ballard et al. 2000 (2); Kamdar 2013 (5); Tolumaru 2006 (7)	NA	He et al. 2015 (3)
Study populations	Nurses, teachers, textile workers, health insurance cohorts, radio/telegraph operators, military, employees of multiple types of companies; company based occupational cohorts; national cohorts of workers, Twins, geographically based populations, participants in control arms of large scale clinical trials (e.g., WHI), hospital/health center populations	Flight attendants	Nurses, clinical population, general population	Ecological, general population of countries around the globe; non-shiftworkers (Israel) recruited in hospitals (BRCA) and friends/convenience sample of cases
Study designs	1 registry study, 7 prospective cohort studies, 22 (case control studies (12 population	~17 registry studies, retrospective cohorts, prospective cohorts, nested	4 studies - 1 prospective cohort (Ramin C 2013); 2 case-control (hospital (Wirth	5 Ecologic (164 countries (Kloog et al. 2008, 2010; 180 countries (Rybnikova N et al.

	Circadian Disruption Proxies			
	Studies of shift workers and shift rotations	**Flight attendants - Transmeridian travel**	**Chronotype as main exposure**	**Artificial Light at Night (ALAN) - impact of the timing and intensity/type of ALAN**
	based, 1 hospital based, 9 nested); 3 studies of Nurses without specific information on shiftwork.	case-controls	MD 2014); and population based Papantoniou K 2015)) and 1 survival study of progression and disease-free interval among brca patients(Hahm BJ 2014).	2015); Israel (Kloog et al. 2008); Korea (Kim RJ et al. 2016), 1 prospective cohort (Hurley et al. 2014); 6 population based case-control (Kloog et al. 2011; Keshet-Sitton et al. 2015; Davis S et al. 2001, Li Q et al. 2010; Bauer SE et al. 2013; Fritschi L et al. 2013))
Location	Asia (Japan, China, Taiwan, Singapore, Shanghai), U.S., Canada, countries in Northern and Southern Europe, Israel, Australia	U.S. and Europe	U.S., Denmark, Spain, India	U.S.(Northeast, Northwest, Georgia, California), Israel, Korea satellite images from 164 countries and updated for 180 countries
Exposure metrics	Ever/never night sw, duration; graveyard shift (midnight to 5am); day/night/rotating shifts; rotating shifts; permanent night shifts; lifetime night shiftwork; JEM for shift schedules **(Pronk et al. 2010; Fernandez et al. 2014**); alternative definitions of prolonged shift work **(Grundy a 2013)**, lifetime average of consecutive night shifts **(Lie 2011)**; years of night shift roation; total	Most studies include only ever employed compared to general populations; JEMs used to determine SW schedules; number of flight hours during the standard sleep interval, and number of time zones crossed using algorithms by Grajewski et al., 2003, 2004, 2011; Waters et al., 2009; Johnson CY et al. 2015	'Morningness-eveningness' questionnaire (MEQ) (Horne & Ostberg, 1976); composite scale of morningness; Questions such as: "One hears about morning and evening types of people. Which ONE of these types do you consider yourself to be?" definitely a morning type", "more of a morning than an evening type", "more of an evening than a morning type", "definitely an evening type", and "neither" (in that	**TIMING OF ALAN:** Light in the sleeping habitat, keeping lights on while sleeping, sleeping mainly in the daytime; not drawing the curtains/window shades while sleeping at night; turning lights on during sleep hours; light habits and lifestyle in the 5 yrs, 15-20 years prior to diagnosis (Cases), or for a 5-yr period 10-15 years prior to study enrollment (controls) - falling asleep with TV on, or turning it off prior to sleep;

	Circadian Disruption Proxies			
	Studies of shift workers and shift rotations	Flight attendants - Transmeridian travel	Chronotype as main exposure	Artificial Light at Night (ALAN) - impact of the timing and intensity/type of ALAN
	number of nights worked; jobs classified as to the % of night shift workers; lifetime cum duration; frequency; occasional and regular night work (hours and duration); ever work in a hospital, medical/surgical ward, maternity/pediatric ward; linking reported occupation to shift work probability (Pshift work) value using exposure assessment recently developed from by Statistics Canada. JEM for categorizing SW in occupations **(RC Fernandez 2014**); Phase Shift **(Fritschi 2013) c**lassification: Forward rotation (night follows day shifts) involves adaptation of central cycle to night shift work; backward rotation (day shifts follow night shifts), or no pattern of shift schedule, or >2 days off between finishing day and starting night shift, assumes unadapted peripheral rhythms. Hi Exposure - job involves >4 nights forward		order); (Munich chronotype questionnaire**); sleep-wake log	exposure to outdoor and indoor light in sleeping habitat; use of bed lamps or room lamps for reading before sleep. **INTENSITY/TYPE OF ALAN:** 1) The subject wore a mask to keep out light; 2) she could not see her hand in front of her face; 3) she could see to the end of her bed; 4) she could see across the room; 5) she could barely read; and 6) she could read comfortably; bedroom-light intensity; type of illumination source for bedroom light and reading light (pictures of flourescent, halogen, and incandescent bulbs shown); Hi exposure: read easily at night at work, Medium exposure - could see but not well enough to read at work; low exposure - had enough light to read in their bedroom when sleeping during the day; not sleeping in total darkness. **ALAN LIGHT POLLUTION / INTENSITY:** percent urban,

	Circadian Disruption Proxies			
	Studies of shift workers and shift rotations	**Flight attendants - Transmeridian travel**	**Chronotype as main exposure**	**Artificial Light at Night (ALAN) - impact of the timing and intensity/type of ALAN**
	rotation or >6 nights backward rotation; Medium exposure: 3–4 nights forward or 4–6 nights backward rotation; Low exposure: 3 nights backward rotation. (Unknown study): circadian phase recording using a temperature data logger to measure wrist skin temperature; partly or entirely working between 00:00 and 6:00a.m. at least three nights per month **(Papantoniou K et al. 2015).**			electricity consumption by country; DMSP-OLS Nighttime Light Time Series satellite images; low (0-20 watts per sterradian cm(2)), medium (21-41 watts per sterradian cm(2)), high (>41 watts per sterradian cm(2).
Confounders and effect modifiers	*in situ* cancers (Schernhammer 2005); estrogen and progestagen receptor positive tumors (Papantoniou et al. 2015; Rabstein S et al. 2013); race (Li W et al. 2015); night work prior to first full term pregnancy (Menegaux F 2013); age; menopausal status; Chronotype (Hansen and Lassen et al. 2012; Wirth MD et al. 2014). Case-control study of cancer in India: Role of PERIOD3 clock gene length polymorphism and	Cosmic Radiation, UV light	ER status; tumor type; PER3 VNTR polymorphism; menopausal status; mis-alignment of bedtime with preferred chronotype	Race (Bauer et al. 2013); BMI and menopausal status (Hurley et al. 2014); polymorphisms (Stevens RG. 2009a. Working against our endogenous circadian clock: cancer and electric lighting in the modern world).

	Circadian Disruption Proxies			
	Studies of shift workers and shift rotations	Flight attendants - Transmeridian travel	Chronotype as main exposure	Artificial Light at Night (ALAN) - impact of the timing and intensity/type of ALAN
	chronotype.); Polymorphisms (Rabstein S et al 2014; GENICA Consortium. Polymorphisms in circadian genes, night work and breast cancer; Truong T et al. 2014, Breast cancer risk, nightwork, and circadian clock gene polymorphisms. Zienolddiny S et al 2013. Analysis of polymorphisms in the circadian-related genes and breast cancer risk in Norwegian nurses working night shifts. Grundy A, et al. 2013, Shift work, circadian gene variants and risk of breast cancer; Wirth MD et al. 2014. Case-control study of cancer in India: Role of PERIOD3 clock gene length polymorphism and chronotype. Liu et al. 2015. Methylation: Aberrant methylation of miR-34b is associated with long-term shiftwork: a potential mechanism for increased breast cancer susceptibility.			

Table 2. Epidemiologic studies of other cancers and circadian disruption: meta-analyses, study populations, exposure metrics, and counfounders or effect modifiers

	Circadian Disruption Proxies		
	Studies of shift workers and shift rotations	**Flight attendants / crew** / Transmeridian travel**	**Artificial Light at Night - impact of timing and intensity/type of ALAN**
	Prostate cancer		
Meta-analyses/ Reviews (No. studies)	Rao et al. 2015 (8); Sigurdardottir et al. 2012 (16); Yong M et al. 2012 (11 post IARC); Gamble KL, et al. 2011. Davis S et al. 2006 Circadian disruption, shift work and the risk of cancer: a summary of the evidence and studies in Seattle; Costa G et al. 2010.	Raslau et al. 2015 (8); Sigurdardottir et al. 2012(7); Buja A 2005 (9); Ballard et al. 2000 (4)	Sigurdardottir et al. 2012 (1 ecological)
Study populations	5 prospective cohorts; 2 retrospective cohort; 2 population based case control studies conducted in general population, industrial workers, working adults; cross-sectional (PSA levels in NHANES)	17 registry studies of airline pilots, cabin attendants, commercial and military pilots; flightdeck/cockpit crews	Ecological study (Kloog 2009); Case-control study of miners (Girschik et al. 2010)
Exposure metrics	Gapstur et al. 2014: rotating shift vs. fixed schedule ascertained by Qx: Do you work rotating shifts? and What time of day do you start working? Responses were combined to create a single variable for work schedule based on BLS definitions and assuming an 8-hour workday. Rotating schedule workers were those who self identified; others were assumed to work fixed schedules. Fixed daytime workers started work	Ever never employed compared with general population; rarely years employed	**Prostate**: Satellite images - global co-distribution of light - Kloog et al. 2009 (no risk estimates)

	Circadian Disruption Proxies		
	Studies of shift workers and shift rotations	**Flight attendants / crew** / Transmeridian travel**	**Artificial Light at Night - impact of timing and intensity/type of ALAN**
	between 6:00AM and 10:00AM; fixed afternoon/evening workers began 2:00PM to 4:00PM; fixed night workers began 9:00PM to 12Midnight.		
Location	U.S., Canada, Germany, Nordic countries, Japan	U.S., Canada, Sweden, Norway, Britain	164 countries
Confounders and effect modifiers	Chronotype, high risk tumors	NA	NA
	Colo-rectal and other hormonal cancers		
Meta-analyses (No. studies)	NA	NA	NA
Cancers and study populations	**Colorectal:** 5 studies: 2 prospective cohorts Japan (Fujino Y et al. 2007) and U.S. Nurses (Schernhammer E et al. 2003), 1 registry cohort Sweden (Schwartzbaum et al. 2007), 2 population based case-control studies (Montreal, Parent et al. 2012; Spain, Papantoniou et al 2014); **Endometrial:** 1 propective Cohort (NHS) (Viswanathan et al. 2007); **Ovarian**: 1 prospective cohort: ACS - CA Prevention II (Carter et al. 2014); 1 nested CC - NHS II (Poole 2011); Seattle health care workers (Bhatti P et al. 2013)	**Colo-rectal:** 2 studies in airline pilots and cabin crew	**Colon**: Ecological study (Kloog 2009)
Exposure metrics	**Ovarian:** ASC cancer prevention cohort: rotating shift vs. fixed schedule ascertained by Qx: Do you work rotating shifts? and What time of day do you start working?	Ever never employed compared with general population; rarely years employed	**Colon**: Satellite images - global co-distribution of light in 164 countries - Kloog et al. 2009 (no risk estimates)

	Circadian Disruption Proxies		
	Studies of shift workers and shift rotations	**Flight attendants / crew** / Transmeridian travel**	**Artificial Light at Night - impact of timing and intensity/type of ALAN**
	Rresponses were combined to create a single variable for work schedule based on BLS definitions and assuming an 8-hour workday. Rotating schedule workers were those who self identified; others were assumed to work fixed schedules. Fixed daytime workers started work between 6:00AM and 10:00AM; fixed afternoon/evening workers began 2:00PM to 4:00PM; fixed night workers began 9:00PM to 12MN.		
Confounders and effect modifiers	**Endometrial:** Obsesity	NA	NA
Melanoma			
Meta-analyses (No. studies)	NA	San Lorenzo et al. 2015 (19); Buja et al. 2006; Ballard et al. 2000; Sigurdson et al. 2004; Hammer GP et al. 2009	Kvaskoff M, Weinstein P. 2010
Study populations	3 Nurses Cohorts (U.S., Denmark, BC Canada); 1 population based case control (Montreal)	Registry studies: ~7 mortality studies; ~16 incidence studies in airline pilots, cabin attendants, commercial and military pilots; flightdeck/cockpit crews	Melanoma: Beral 1982
Exposure metrics	Ever never worked nights; duration	Registry data - ever/ never employed	NA
Confounders and effect modifiers	none	risk factors in aircrew - Rafnsson F et al. 2003; Kojo K et al. 2013	NA
Other cancers			
Meta-analyses (No. studies)	NA	Ballard et al. 2000 (6); BRAIN: Ballard et al. 2000 (4); ALL	NA

	Circadian Disruption Proxies		
	Studies of shift workers and shift rotations	Flight attendants / crew** / Transmeridian travel	Artificial Light at Night - impact of timing and intensity/type of ALAN
		CANCERS (females): Ballard et al. 2000 (2)	
Cancers	**Liver cancer** (1 cohort Japan, Lin Y et al. 2015); **lung** (1 cohort U.S., Gu F et al. 2015; CC population Montreal, Parent et al. 2012' UK manual workers Taylor et al. 1972); Textile worker Cohort Shanghai, Kwon P et al. 2015; UK manual worker Cohort, Taylor et al. 1972); **bladder** (CC population Montreal, Parent et al. 2012; UK manual worker Cohort Taylor et al. 1972); **stomach** (CC population Montreal, Parent et al. 2012; Cohort, Taylor et al. 1972), **kidney** (1 CC population Montreal), **esophageal** (1 CC population Montreal); **NHL** (Chemical workers Germany, Carreon T et al. 2014; registry Finland (Lahti et al. 2008), CC population Montreal, Parent et al. 2012), **pancreatic** (cohort Japan, Lin Y et al. 2013; CC Montreal, Parent et al. 2012); leukemia (German manufacturers, Yong M et al. 2014; UK manual workers, Taylor et al. 1972); **brain** (Danish nurses, Kjaer T 2009)	**Brain cancer** (Zeeb H 2010; Nicholas JS 1998; Irvine D 1999); **NHL** (Zeeb H 2010; Pinkerton LE 2012); **kidney and renal pelvis** (Nicholas JS 1998); **liver cancer** (Haldorsen T 2001); **AML** (Gundestrup M 1999); several studies reported higher rates of **HIV related cancers** and **oral cancers and upper respiratory tract cancers**.	NA
Study populations	General populationbased CC in Spain, Montreal, Finland; General population cohorts in Japan, Sweden;	Airline pilots, cabin attendants, commercial and military pilots; flightdeck/cockpit crews	**Lung**: Ecological study (Kloog 2009)

	Circadian Disruption Proxies		
	Studies of shift workers and shift rotations	**Flight attendants / crew** / Transmeridian travel**	**Artificial Light at Night - impact of timing and intensity/type of ALAN**
	Occupational cohorts of nurses (U.S.), Chemical manufacturers (U.S.), and textile workers (Shanghai)		
Exposure metrics	Work schedule in longest occupation; "shiftworkers" and "non-shiftworkers (Rana S 2014a, b); **JEMs-**Stenehjem JS 2015; Ji B et al. 2012;Carreon T et al. 2014; Lahti TA et al. 2008	Ever/never compared to general populations; no data on confounders	**LUNG:** Satellite images - global co-distribution of light In 164 countries - Kloog et al. 2009
Confounders and effect modifiers	Polymorphisms: Chronic lymphocytic leukemia (CLL) Rana S 2014 a,b; Glioma (Madden et al. 2014)	NA	NA

Table 3. Biomarkers used in epidemiologic studies of circadian disruption and cancer

CD Proxy	Biomarkers			
	Urinary melatonin levels	Vitamin D levels	Temperature, cortisol, reproductive hormones, receptor status	Circadian clock gene polymorphisms, gene expression, and methylation patterns
		Breast cancer		
Meta-analyses/ Reviews	Basler et al. 2014 (5)	Gandini et al. 2011 (10); Chen et al. 2010 (21); Mohr et al. 2011 (11); van der Rhee et al. 2013 Sunlight (13), in serum (15)	NA	NA
Studies of shift workers	Schernhammer et al. 2005, 2008, 2009, 2010; Travis et al. 2004; Skene et al. 1990; Bartsch et al. 1997; Davis et al. (2012)	Romano A et al. 2015;Grant WB et al. 2015; Itoh H et al. 2011	Cortisol: Niu SF et al. 2015; Amirian I et al. 2015	Fang MZ et al. 2015. Sleep interruption associated with house staff work schedules alters circadian gene expression. Rabstein S et al 2014 Polymorphisms in circadian genes, night work and breast cancer: results from the GENICA study; Zienolddiny S et al. 2013 Associations between polylmorphisms in circadian genes, night work, and brca risk; Grundy et al. 2013 Shift work, circadian gene variants and risk of breast cancer. Davis and Mirick 2006. Circadian disruption, shift work and the risk of cancer. Liu et al. 2015 Aberrant methylation of miR-34b is

CD Proxy	Biomarkers: Urinary melatonin levels	Vitamin D levels	Temperature, cortisol, reproductive hormones, receptor status	Circadian clock gene polymorphisms, gene expression, and methylation patterns
				associated with long-term shiftwork: a potential mechanism for increased breast cancer susceptibility
Studies of the impact of the timing and intensity/ type of ALAN	**Cho Y et al. 2015** Effects of artificial light at night on human health: A literature review of observational and experimental studies applied to exposure assessment. **Haim A and Zubidat AE 2015** Artificial light at night: melatonin as a mediator between the environment and epigenome. **Wang WS et al. 2014** Light exposure at night, sleep duration, melatonin, and breast cancer: a dose-response analysis of observational studies. **Kennaway DJ 2015** Light at night, melatonin and breast cancer. **Haus EL and Smolensky MH 2013.** Shift work and cancer risk: potential mechanistic roles of circadian disruption, light at night, and sleep deprivation. **Reiter RJ et al. 2007** Light at night, chronodisruption,	**Fuhrman BJ et al. 2013** Sunlight, polymorphisms of vitamin D-related genes and risk of breast cancer. **Van der Rhee H** et al. 2013 Is prevention of cancer by sun exposure more than just the effect of vitamin D? A systematic review of epidemiological studies. **Suba Z et al. 2012** Light deficiency confers breast cancer risk by endocrine disorders. **Engel P et al. 2011** Joint effects of dietary vitamin D and sun exposure on breast cancer risk: results from the French E3N cohort. **Proietti S et al. 2011** Melatonin and vitamin D3 synergistically down-regulate Akt and MDM2 leading to TGFβ-1-dependent growth inhibition of breast cancer cells.	NA	**Rabstein S et al. 2014** Polymorphisms in circadian genes, night work and breast cancer: results from the GENICA study.

CD Proxy	Biomarkers			
	Urinary melatonin levels	Vitamin D levels	Temperature, cortisol, reproductive hormones, receptor status	Circadian clock gene polymorphisms, gene expression, and methylation patterns
	melatonin suppression, and cancer risk: a review.			
Sunlight exposure	**Smolensky MH et al. 2015** Nocturnal light pollution and underexposure to daytime sunlight: Complementary mechanisms of circadian disruption and related diseases.	See Meta-analyses/Reviews	NA	**Proietti S et al. 2011** Melatonin and vitamin D3 synergistically down-regulate Akt and MDM2 leading to TGFβ-1-dependent growth inhibition of breast cancer cells.
Other or No CD proxy	**Schernhammer et al. 2005; 2008; 2010** Melatonin and BRCA (various cohorts and menopausal status); **Wu AH et al. 2013** Sleep duration, spot urinary 6-sulfatoxymelatonin levels and risk of breast cancer among Chinese women in Singapore	NA	**Sephton SE 2000** Diurnal **cortisol** rhythm as a predictor of breast cancer survival. **Ticher A 1996** The pattern of hormonal circadian time structure (acrophase) as an assessor of breast-cancer risk. **Lewy H 2007.** Linkage between ability to change period tau of Prolactin and **cortisol** rhythms and brca risk; **Lie et al. 2013** Night work and Hormone receptor status; **Zeitzer JM et al. 2014** Correspondence of plasma and salivary cortisol patterns in women with breast cancer.	**Polymorphisms. Wang WM et al. 2013** [Association of genetic variantions of circadian clock genes and risk of cancer]; **Dai H, et al. 2011**, The role of polymorphisms in circadian pathway genes in breast tumorigenesis. **Hoffman AE, 2010**. CLOCK in breast tumorigenesis: genetic, epigenetic, and transcriptional profiling analyses**.** **Krugluger W et al. 2007** Regulation of genes of the circadian clock in human colon cancer: reduced period-1 and dihydropyrimidine dehydrogenase transcription correlates in high-grade

CD Proxy	Biomarkers: Urinary melatonin levels	Vitamin D levels	Temperature, cortisol, reproductive hormones, receptor status	Circadian clock gene polymorphisms, gene expression, and methylation patterns
				tumors.
Prostate cancer				
Meta-analyses/ Reviews	NA	**Gandini et al. 2011 (11); van der Rhee et al. 2013 Sunlight (9), in serum (16); Gilbert R et al. 2011**	NA	NA
Studies of shift workers	NA	NA	Flynn-Evans EE 2013 Shift work and PSA levels	
Studies of intensity/ type of ALAN		NA	NA	**DeHaro D et al. 2014.** Regulation of L1 expression and retrotransposition by melatonin and its receptor: implications forcancer risk associated with light exposure at night
Sunlight exposure	NA	See Meta-analyses/Reviews	NA	NA
Other or No CD proxy	Bartsch C, 1992; **Markt S et al 2014 G**ene-based associations with fatal prostate cancer and melatonin levels; **Sigurdardottir LG et al. 2015** Urinary melatonin levels, sleep disruption, and risk of prostate cancer in elderly men. **Erren TC et al. 2015** Melatonin, sleep, and prostate cancer in elderly men: study, hypothesis	NA	NA	**Jung-Hynes B et al. 2010** Melatonin resynchronizes dysregulated circadian rhythm circuitry in human prostate cancer cells.

CD Proxy	Biomarkers Urinary melatonin levels	Vitamin D levels	Temperature, cortisol, reproductive hormones, receptor status	Circadian clock gene polymorphisms, gene expression, and methylation patterns
	development, and icelandic options.			
Colo-rectal and other hormonal cancers				
Meta-analyses/ Reviews	NA	**Colorectal:** Gandini et al. 2011 (9); Touvier M. et al. 2011; van der Rhee et al. 2013, Sunlight (7), in serum (12); **Endometrial** - McCullough et al., 2008	NA	NA
Studies of shift workers	**Ovarian:** Poole et al. 2015	NA	NA	NA
Studies of intensity/ type of ALAN	NA	NA	NA	NA
Sunlight exposure	NA	See Meta-analyses/Reviews	NA	NA
Other or No CD proxy	NA	Endometrial - van der Rhee et al. 2009	Mormont MC 2000 (Colorectal cancer)	**Polymorphisms**. **Colorectal: Alexander M, et al. 2015**. Case-control study of the PERIOD3 clock gene length polymorphism and colorectal adenoma formation; **Karantanos T, 2013,** Association of the clock genes polymorphisms with colorectal cancer susceptibility; **Zhou F, et al. 2012**. Functional polymorphisms of circadian positive feedback regulation genes and clinical outcome of

CD Proxy	Urinary melatonin levels	Vitamin D levels	Temperature, cortisol, reproductive hormones, receptor status	Circadian clock gene polymorphisms, gene expression, and methylation patterns
				Biomarkers
				Chinese patients with resected colorectal cancer; **Ovarian cancer: Jim HS et al. 2015.** Common Genetic Variation in Circadian Rhythm Genes and Risk of Epithelial Ovarian Cancer (EOC).
		Other cancers		
Meta-analyses/ Reviews	NA	NA	NA	NA
Studies of shift workers	**CLL:** Rana S 2014a,b	**NHL**: van der Rhee et al. 2013, Sunlight (23), in serum (4).	NA	**CLL - Rana S, et al. 2014a,b.** a) Lack of association of the NPAS2 gene Ala394Thr polymorphism (rs2305160:G>A) with risk of CLL; b) Deregulated expression of circadian clock and clock-controlled cell cycle genes in CLL
Studies of intensity/ type of ALAN	NA	NA	NA	NA
Sunlight exposure	NA	**NHL:** Van der Rhee et al. 2013 - Sunlight (23), in serum (4); Van der Rhee et al. 2009 - In serum, prospective: pancreatic (3); esophageal (3); renal (1)*	NA	NA

	Biomarkers			
CD Proxy	**Urinary melatonin levels**	**Vitamin D levels**	**Temperature, cortisol, reproductive hormones, receptor status**	**Circadian clock gene polymorphisms, gene expression, and methylation patterns**
Other or No CD proxy	NA	NA	NA	**Non-small cell Lung CA - Couto P 2014;** Polymorphisms in the CCRN4L and PER3 genes may be risk factor Liver Cancer - Zhao B et al. 2012

Table 4. Biomarkers/markers used in exposure studies of proxies of circadian disruption

Biomarker	Proxy of circadian disruption
	Shift work, transmeridian travel
Melatonin	**Bracci et al. 2014** Rotating-shift nurses after a day off: peripheral clock gene expression, urinary melatonin, and serum 17-β-estradiol levels; **Bhatti et al. 2013** Racial differences in the association between night shift work and melatonin levels among women.**Mirick et al. 2013** Night shift work and levels of 6-sulfatoxymelatonin and cortisol in men; **Grundy et al. 2009** Light intensity exposure, sleep duration, physical activity, and biomarkers of melatonin among rotating shift nurses; **Grundy et al. 2011 I**nfluence of light at night exposure on melatonin levels; **Papantoniou et al. 2015** 16 hormones, M and F - Increased and mistimed sex hormone production in night shift workers; **Papantoniou K et al. 2014** Circadian variation of melatonin, light exposure, and diurnal preference in day and night shift workers of both sexes; **Gomez-Acebo et al. 2015** Association between exposure to rotating night shift versus day shift - melatonin and cortisol and other sex hormones in women; **Ji B et al. 2012** Nightshift work job exposure matrices and urinary 6-sulfatoxymelatonin levels among healthy Chinese women; **Langley et al. 2012** A cross-sectional study of breast cancer biomarkers among shift working nurses; **Dumont M et al. 2014** Progressive decrease of melatonin production over consecutive days of simulated night work; **Zamanian Z et al. 2013** Outline of changes in cortisol and melatonin circadian rhythms in the security guards of shiraz university of medical sciences; **van de Werken M et al. 2013; Reinhardt ÉL et al. 2012** Daily rhythm of salivary IL-1ß, cortisol and melatonin in day and night workers**; Amirian I et al. 2015**
Cortisol	**Mirick et al. 2013** Night shift work and levels of 6-sulfatoxymelatonin and cortisol in men**; Papantoniou et al 2015** (16 hormones) males and females - Increased and mistimed sex hormone production in night shift workers; **Gomez-Acebo et al. 2015** Association between exposure to rotating night shift versus day shift - melatonin and cortisol and other sex hormones in women; **Wirth M, et al. 2013.** Association of the Period3 clock gene length polymorphism with salivary cortisol secretion among police officers. **Niu SF et al. 2015; Amirian I et al. 2015; Baba M 2015**; **Costa G et al. 2015** Stress and sleep in nurses employed in "3 × 8" and "2 × 12" fast rotating shift schedules; **Fekedulegn D 2012** Associations of long-term shift work with waking salivary cortisol concentration and patterns among police officers. **Zamanian Z et al. 2013** Outline of changes in cortisol and melatonin circadian rhythms in the security guards of shiraz university of medical sciences**; Reinhardt ÉL et al. 2012** Daily rhythm of salivary IL-1ß, cortisol and melatonin in day and night workers
Vitamin D	**Wallingford et al. 2014** UV and dietary predictors of serum 25-hydroxyvitamin D concentrations among young shift-working nurses in Canada; **Romano A et al. 2015** Shift work and serum 25-OH vitamin D status among factory workers in Northern Italy
Sex steroid hormones, prolactin	**Papantoniou et al 2015** (16 hormones) males and females; **Gomez-Acebo et al. 2015** (females); **Bracci et al. 2014** Rotating-shift nurses after a day off: peripheral clock gene expression, urinary melatonin, and serum 17-β-estradiol levels**; Chang YS et al. 2014** Rotating night shifts too quickly may cause anxiety and decreased attentional performance, and impact prolactin levels during the subsequent day: a case control study.
Clock gene	**An H 2014** Chronotype and a PERIOD3 variable number tandem repeat polymorphism in Han Chinese pilots. **Wirth M, et al.**

Biomarker	Proxy of circadian disruption
polymorphisms, clock gene expression, methylation	**2013**. Association of the Period3 clock gene length polymorphism with salivary cortisol secretion among police officers. **Bracci et al. 2014** Rotating-shift nurses after a day off: peripheral clock gene expression, urinary melatonin, and serum 17-β-estradiol levels; **Zhu Y et al. 2011** Long-term exposure to shiftwork can alter epigenetic patterns genome wide; **Bracci et al. 2013** Influence of night-shift and napping at work on urinary melatonin, 17-β-estradiol and clock gene expression in pre-menopausal nurses; **Reszka et al. 2013** Circadian gene expression in peripheral blood leukocytes of rotating night shift nurses.
Lifestyle, dietary factors, demographics, joint factors	**Kjaer T et al. 2014** Dietary inflammation index from FFQ and Shiftwork; **Fernandez RC et al. 2014** JEM for SW, LAN, Sleep, Diet, Physical Activity, and Vit D; **Wirth MD et al. 2014** Association of a dietary inflammatory index with inflammatory indices.
plasma alanine transaminase (ALT) levels	**Lin YC 2014** Long term rotating shift work poses a barrier to normalization of alanine transaminase
physical stress	**Monteleone P 1992a, b**
Markers of immune response (e.g., IL-6, TNF-alpha, cytokene levels, lymphocyte counts)	**van Mark et al. 2010**; **Khaleghipour S et al**. Circadian type, chronic fatigue, and serum IgM in SW; **Copertaro A et al. 2011** immune variables in nurses
	Artificial light / ALAN
Melatonin, phase shift	**Kozaki T et al. 2016** Light-induced melatonin suppression at night after exposure to different wavelength composition of morning light. **Kozaki T et al. 2015** Effects of day-time exposure to different light intensities on light-induced melatonin suppression at night. **Emens JS 2015** Effect of Light and Melatonin and Other Melatonin Receptor Agonists on Human Circadian Physiology. **Cho Y et al. 2015** Effects of artificial light at night on human health: A literature review of observational and experimental studies applied to exposure assessment. **Grundy et al. 2009** (Light intensity exposure, sleep duration, physical activity, and biomarkers of melatonin among rotating shift nurses); **Grundy et al. 2011** (influence of light at night exposure on melatonin levels)**; Leproult R 2001** Transition from dim to bright light in the morning induces an immediate elevation of cortisol levels**; Hurley S 2013** A cross-sectional analysis of light at night, neighborhood sociodemographics and urinary 6-sulfatoxymelatonin concentrations; **Burgess HJ, Molina TA. 2014** Home lighting before usual bedtime impacts circadian timing: a field study**; Higuchi S et al. 2014** Influence of light at night on melatonin suppression in children**; Papantoniou K et al. 2014** Circadian variation of melatonin, light exposure, and diurnal preference in day and night shift workers of both sexes**; Ho Mien I et al. 2014** Effects of exposure to intermittent versus continuous red light on human circadian rhythms, melatonin suppression, and pupillary constriction**; van de Werken M et al. 2013** Short-wavelength attenuated polychromatic white light during work at night**; Obayashi K et al. 2012** (daylight in elderly); **Wood B et al. 2013** (light from tablets); **Chang AM et al. 2012** (bright light of different durations); **Graham C 2001**

Biomarker	Proxy of circadian disruption
	Examination of the melatonin hypothesis in women exposed at night to EMF or bright light. **Burke TM et al. 2013** Combination of light and melatonin time cues for phase advancing the human circadian clock; **Visser EK et al. 1999** Melatonin suppression by light in humans is maximalwhen the nasal part of the retina is illuminated.
Cortisol	**Leproult R 2001** Transition from dim to bright light in the morning induces an immediate elevation of cortisol levels; **Zamanian Z et al. 2013**
Body temperature	**Te Kulve M et al. 2016** Review
Lifestyle, dietary factors, demographics, joint factors	**Fernandez RC et al. 2014** JEM for SW, LAN, Sleep, Diet, Physical Activity, and Vit D
	Chronotype or circadian disruption
Methodologic / marker development	**Kantermann T et al. 2015** compares 2 Chrono QX with DMSO; **Simpkin CT et al. 2014** compares parent chrono qx with salivary melatonin in toddlers; **Van Dycke KC 2015** Biomarkers for circadian rhythm disruption independent of time of day. **Kantermann T 2015** Comparing the Morningness-Eveningness Questionnaire and Munich ChronoType Questionnaire to the Dim Light Melatonin Onset. **Burgess HJ et al. 2015** Home circadian phase assessments with measures of compliance yield accurate dim light melatonin onsets. **Papantoniou K et al. 2014; Garaulet M et al. 2015** Methods for measuring CD; **Figueiro MG et al. 2013 C**omparison of three practical field devices to measure personal light exposures and activity levels.
Melatonin	**Papatoniou K et al. 2014;** Bhatti P et al. 2014; Bracci M 2014 (role of chronotype shown to be independent factor for PER1 (β 0.48, P=0.001) and PER2 (β -0.22, P=0.022) expression, and 17-β-estradiol levels (β 0.26, P=0.011)
Other hormones	**Bracci M 2014** chronotype an independent risk factor for 17β estradiol levels
Clock gene expression	**Bracci M 2014** chronotype an independent risk factor for PER1 and PER2 gene expression
Clock gene polymorphisms	**An H 2014** Chronotype and a PERIOD3 variable number tandem repeat polymorphism in Han Chinese pilots
Lifestyle, dietary factors, demographics, joint factors	**Bhatti P et al. 2013** (Asian and Caucasian SW), **Zhang L. et al. 2015** (Amish); **Smith MR, et al. 2009** Racial differences I human endogenous circadian period; **Eastman CI et al. 2012** Blacks have shorter free-running periods than whites
Markers of immune response (e.g., IL-6, TNF-alpha, cytokene levels, lymphocyte counts)	**Labrecque N et al. 2015** Circadian clocks in the immune system

Biomarker	Proxy of circadian disruption
	Lifestyle factors and Non-photic entrainment sources
Exercise	**Monteleone P et al. 1992; Yamanaka Y et al. 2015; Grundy et al. 2009** (Light intensity exposure, sleep duration, physical activity, and biomarkers of melatonin among rotating shift nurses;**Barger LK** et **al 2004** Daily exercise facilitates phase delays of circadian melatonin rhythm in very dim light. **Mistlberger RE and Skene DJ 2005** Nonphotic entrainment in humans?
Diet	**Fukushige H et al.** Tryptophan-rich breakfast and light exposure on Melatonin; **Mistlberger RE and Skene DJ 2005** Nonphotic entrainment in humans; **McHill AW et al. 2014** Effects of caffeine on skin and core temperatures, alertness, and recovery sleep during circadian misalignment.

Table 5. Laboratory, clinical, and field studies of melatonin, light, and shiftwork interventions in relation to long term disease endpoints

SHIFT WORK: Changes in direction, speed, length, and other adjustments to rotating shifts	
Reviews/meta-analyses	**Neil-Sztramko SE 2014** Prospective interventions conducted among shift workers with the aim of improving long-term healthchanges in shift schedules; 16 studies describing changes in direction of rotation from backward (counter-clockwise) to forward (clockwise) rotating shift (6 studies) and vice versa (1 study); switching from 8- to 10- or 12-hour shifts (6 studies); adjusting the shift schedule based on ergonomic principles (1 study); flexible shift scheduling (1 study); delaying shift start time (1 study). Changes from backward to forward rotating shifts increased rotation speed in 4 studies. **Bambra CL 2008** - Systematic review of experimental and quasi-experimental studies, from any country (in any language) that evaluated the effects on health and work-life balance of organizational-level interventions that redesign shift work schedules; **Zee PC and Goldstein CA 2010** Treatment of shift work disorder and jet lag.
Endpoint 1: Sleep quantity/duration, quality	Boggild et al 2001; Hakola et al 2001; Hakola et al 2010; Harma et al. 2006; Karlson et al 2009; Knauth et al. 1998; Lowden et al 1998; Orth-Gomer 1982, 1983; Peacock et al 1983; Rosa et al. 1989; Viitasalo et al. 2008; Williamson et al, 1994.
Endpoint 2: Markers of circadian disruption/adaptation	Peacock et al. 1983; Waage S 2014 Longitudinal study on determinants of shift work disorder
Endpoint 3: common modifiable risk factors for chronic disease (unhealthy diet and excessive energy intake; physical inactivity; tobacco use)	Boggild et al. 2001; Orth-Gomer et al. 1982, 1983; Viitasalo et al 2008; Jarvelin-Pasanen et al. 2013
Endpoint 4: common modifiable risk factors for chronic disease (unhealthy diet and excessive energy intake; physical inactivity; tobacco use)	Boggild et al. 2001; Hakola et al. 2010; Knauth et al. 1998; Peacock et al. 1983; Rosa et al. 1989; Viitasalo et al. 2008

LIGHT: Controlled exposure to light and dark (e.g., exposure to bright light in the workplace, use of goggles to minimize bright light exposure	
Reviews/meta-analyses	**Neil-Sztramko SE 2014 -** prospective interventions conducted among shift workers with the aim of improving long-term healthchanges in shift schedules - reviewed 17 studies of controlled exposure to light and dark (e.g., exposure to bright light in the workplace, use of goggles to minimize bright light exposure or short wavelengths); with 13 interventions of controlled light exposure among shiftworkers - among these, intermittent bright light was evaluated in 7 studies; combination of bright light and light blocking goggles was used in 4 studies; two studies used glasses that filtered blue light wavelengths. **Burgess HJ 2002** - Bright light, dark and melatonin as interventions in shift workers; qualitative review. **Fonken LK et al. 2014**. Exposure to light at night alters metabolic function through disruption of the circadian system,

LIGHT: Controlled exposure to light and dark (e.g., exposure to bright light in the workplace, use of goggles to minimize bright light exposure	
	and review current experimental and epidemiological work directly associating exposure to light at night and metabolism.
Endpoint 1: Sleep quantity/duration, quality	Bjorvatn et al 1999; Bjorvatn et al. 2007; Boivin et al 2012; Budnick et al 1995; Lowden et al. 2004; Sasseville et al 2009, 2010; Tanaka et al 2011; Thorne et al 2010; Rahman et al. 2013.
Endpoint 2: Markers of circadian disruption/adaptation (phase shift)	MELATONIN: Lewy AJ et al 1996 Phase shifting the human circadian clock using melatonin; Lewy AJ et al. 2006 Circadian uses of melatonin in humans; Lewy AJ et al. 1995 Melatonin marks circadian phase position and resets the endogenous circadian pacemaker in humans; Boivin et al. 2002, 2004, 2012; Brainard GC et al. 2001; Budnick et al. 1995; Deacon SJ et al. 1994 phase-shifts in melatonin, 6-sulphatoxymelatonin and alertness rhythms after treatment with moderately bright light at night. DIjk D et al. 2012 Amplitude reduction and phase shifts of melatonin, cortisol and other circadian rythms after gradual advance of sleep and light exposure; Kakooei et al. 2010; Lowden et al. 2004; Sasseville et al. 2010; Thorne et al. 2010; Young CR 2015; Brainard GC et al. 2015; Crowley SJ et al. 2015 Phase advancing human circadian rhythms with morning bright light, afternoon melatonin, and gradually shifted sleep; Chang AM et al. 2015; Figueiro MG et al. 2014a,b; Sano I et al. 2014; Kim SJ et al. 2014; CORTISOL: James et al. 2004; Zamanian et al 2010; and BODY TEMPERATURE Boivin et al 2002, 2004; Kakooei et al. 2010); Litscher D et al. 2013. PLASMA THYROTROPIN: Hirschfeld U et al. Progressive elevation of plasma thyrotropin during adaptation to simulated jet lag.
Endpoint 3: common modifiable risk factors for chronic disease (unhealthy diet and excessive energy intake; physical inactivity; tobacco use)	Obayashi K et al. 2014 (BP); Litscher D et al. 2013 (heart rate)
Endpoint 4: common modifiable risk factors for chronic disease (unhealthy diet and excessive energy intake; physical inactivity; tobacco use)	NA

BEHAVIOR OR LIFESTYLE: Dietary changes, physical acivity, scheduled napping, cognitive behavioral therapy	
Reviews/meta-analyses	Neil-Sztramko SE 2014 - prospective interventions conducted among shift workers with the aim of improving long-term healthchanges in shift schedules; 5 interventions
Endpoint 1: Sleep quantity/duration, quality	Bonnefond et al. 2001; Harma et al. 1988a; Smith-Coggins et al 1997; Jarnefelt H. et al. 2012.
Endpoint 2: Markers of circadian disruption/adaptation	Harma et al. 1988b; Fukushige H et al. 2014
Endpoint 3: Markers of chronic disease (Raised blood pressure, raised blood glucose, abnormal	Harma et al. 1988a; Morgan et al. 2011

BEHAVIOR OR LIFESTYLE: Dietary changes, physical acivity, scheduled napping, cognitive behavioral therapy	
blood lipids, overweight/obesity	
Endpoint 4: common modifiable risk factors for chronic disease (unhealthy diet and excessive energy intake; physical inactivity; tobacco use)	Morgan et al. 2011a,b; Jarnefelt H. et al. 2012

PHARMACOLOGIC: Interventions to modify Endpoints #1-4 (e.g., Modafinil, Armodafinil, Zopiclone, melatonin)	
Reviews/meta-analyses	**Burgess HJ 2002** (2 studies); **Neil-Sztramko SE 2014** (8 studies); **Richardson G and Tate B** 2000 Hormonal and pharmacological manipulation of the circadian clock: recent developments and future strategies;
Endpoint 1: Sleep quantity/duration, quality	**MELATONIN**: Bjorvain et al. 2007; Cavallo et al 2005; Folkard et al.1993; Turek FW and Gillette MU 2004 Melatonin, sleep and circadian rhythms: rationale for development of specific melatonin agonists; ; **Modafinil or armodafinil:** Czeisler et al. 2005; Czeisler et al. 2009; Erman et al. 2007; ZOPICLONE: (Bozin-Juracic et al 1996; Monchesky et al 1989); **BENZODIAZEPINE**: **Turek FW 1988** Manipulation of a central circadian clock regulating behavioral and endocrine rhythms with a short-acting benzodiazepine used in treatment of insomnia.
Endpoint 2: Markers of circadian disruption/adaptation	**Modafinil:** Czeisler et al. 2005); MELATONIN: Sharkey KM and Eastman CI 2002 Melatonin phase shifts human circadian rhythms in a placebo-controlled simulated night-work study; **BENZODIAZEPINE: Buxton OM** et al. 2000 Benzodiazepine hypnotic facilitates adaptation of circadian rhythms simulating westward jet lag; Wisor JP 2002 Disorders of the circadian clock: etiology and possible therapeutic targets.
Endpoint 3: Markers of chronic disease (Raised blood pressure, raised blood glucose, abnormal blood lipids, overweight/obesity	**Armodafinil:** Czeisler et al. 2009; MELATONIN: Bizzarri M 203 Melatonin and vitamin D3 increase TGF-beta1 release and induce growth inhibition in breast cancer cell cultures.
Endpoint 4: common modifiable risk factors for chronic disease (unhealthy diet and excessive energy intake; physical inactivity; tobacco use)	**Hrushesky WJ, et al. 2009** Circadian clock manipulation for cancer prevention and control and the relief of cancer symptoms.
Endpoint 5: timing of chemotherapy and other medications to maximize efficacy	**Innominato PF et al. 2014** The circadian timing system in clinical oncology. **Ortiz-Tudela E et al. 2013** Cancer chronotherapeutics: experimental, theoretical, and clinical aspects; **Košir R et al**. 2013 Circadian events in human diseases and in cytochrome P450-related drug metabolism and therapy.